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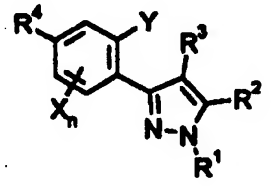
(54) Title: HERBICIDAL PYRAZOLE COMPOUNDS

(57) Abstract



(I)

Compounds of general formula (I), wherein R^1 is hydrogen or alkyl, alkenyl, alkynyl, benzyl, cycloalkyl or cycloalkenyl, any of which may optionally be substituted; R^2 is alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or halo, OR^5, SO_mR^5, $O(alkyl)CO_2R^5$ or $O(alkyl)COR^5$; m is 0, 1 or 2; R^3 is H, halogen, cyano, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or SO_2Z, COR^5, CO_2R^5 or OR^5; R^4 is H, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or cyano, nitro, halogen, NR^5R^6, OR^5, SO_pR^5, CO_2R^5, $CONR^5R^6$, $NR^5SO_2R^6$, COR^5, $C(NOR^5)R^6$, OSO_pR^5, NR^5COR^6, $O(alkyl)COR^5$, $O(alkyl)CO_2R^5$ or SO_2Z; each X is independently halogen, cyano, nitro, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, OR^5, NR^5R^6, $NR^5SO_2R^6$, OSO_2R^5, SO_pR^5, CO_2R^5, COR^5, NR^5COR^6, R^5OR^6, $CONR^5R^6$, SO_2Z or heterocyclyl or, alternatively two X groups or an X group and R^4 may together form a further ring; Z is halogen; p is 0, 1 or 2; n is 0, 1, 2 or 3; Y is halogen, cyano or optionally substituted alkoxy; R^5 and R^6 are each independently H, alkyl, alkenyl or alkynyl, any of which may optionally be substituted; are active as herbicides and are effective when applied either pre- or post-emergence.

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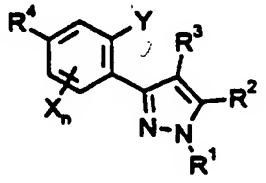
HERBICIDAL PYRAZOLE COMPOUNDS

This invention relates to chemical compounds useful as herbicides, to processes for preparing them, and to herbicidal compositions and processes utilising them.

Herbicidal compounds based upon aryl pyrazoles are known, for example from J03072460 and WO92/06962.

The applicants have found a group of compounds which have a particular substituent pattern and which are active as herbicides.

According to the present invention, there is provided a compound of formula (I):



I

wherein:

R^1 is hydrogen or alkyl, alkenyl, alkynyl, benzyl, cycloalkyl or cycloalkenyl, any of which may optionally be substituted;

R^2 is alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or halo, OR^5, SO_mR^5, $O(alkyl)CO_2R^5$ or $O(alkyl)COR^5$;

m is 0, 1 or 2;

R^3 is H, halogen, cyano, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or SO_2Z, COR^5, CO_2R^5 or OR^5;

R^4 is H, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or cyano, nitro, halogen, NR^5R^6, OR^5, SO_pR^5, CO_2R^5, $CONR^5R^6$, $NR^5SO_2R^6$, COR^5, $C(NOR^5)R^6$, OSO_pR^5, NR^5COR^6, $O(alkyl)COR^5$, $O(alkyl)CO_2R^5$ or SO_2Z;

Each X is independently halogen, cyano, nitro, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, OR^5, NR^5R^6, $NR^5SO_2R^6$, OSO_2R^5, SO_pR^5, CO_2R^5, COR^5, NR^5COR^6, R^5OR^6, $CONR^5R^6$, SO_2Z or heterocyclyl or, alternatively two X groups or an X group and R^4 may together form a further ring;

Z is halogen;

p is 0, 1 or 2;

n is 0, 1, 2 or 3;

Y is halogen, cyano or optionally substituted alkoxy;

R^5 and R^6 are each independently H, alkyl, alkenyl or alkynyl, any of which may optionally be substituted.

As used herein, the term "alkyl" refers to straight or branched fully saturated hydrocarbon chains having up to 10 carbon atoms. The term "lower" used in relation to "alkyl" means that the chains have from 1 to 4 carbon atoms.

Similarly, the term "alkenyl" refers to a straight or branched hydrocarbon chain having at least one double bond and having up to ten carbon atoms and the term "alkynyl" refers to a straight or branched hydrocarbon chain having at least one triple bond and up to ten carbon atoms. The term "lower" used in relation to alkenyl and alkynyl means that the chains have from two to four carbon atoms.

Terms such as "alkoxy", "haloalkyl" and "haloalkenyl" should be construed in accordance with the definitions for alkyl, alkenyl and alkynyl. Such groups have up to ten carbon atoms unless used in conjuction with the term "lower" when they have up to four carbon atoms.

The term "cycloalkyl" as used herein refers to a saturated hydrocarbon ring having from three to eight ring carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl and cyclohexyl.

The term "cycloalkenyl" as used herein refers to a hydrocarbon ring having from three to eight ring carbon atoms and containing at least one double bond. Examples of such groups include cyclohexenyl.

The term "halogen" used herein includes fluorine, chlorine, bromine and iodine.

Suitable optional substituents for alkyl, alkenyl, alkynyl, alkoxy, benzyl, cycloalkyl and cycloalkenyl, groups described herein include cyano; nitro; halogen such as chlorine, fluorine and bromine; haloalkyl such as trifluoromethyl; carboxylic ester groups such as carboxymethyl or carboxyethyl; substituted and unsubstituted carboxamides such as N,N-dimethylamido; alkoxy, in particular haloalkoxy such as trifluoromethoxy; aryl such as phenyl or naphthyl; cycloalkyl for examples containing up to 7 ring atoms; or heterocyclyl containing for example up to 10 ring atoms, up to three of which are selected from oxygen, nitrogen and sulphur, such as tetrahydrofuryl.

The formula (I) given above is intended to include tautomeric forms of the structure drawn, as well as physically distinguishable modifications of the compounds which may arise,

for example, from different ways in which the molecules are arranged in a crystal lattice, or from the inability of parts of the molecule to rotate freely in relation to other parts, or from geometrical isomerism, or from intra-molelcular or inter-molecular hydrogen bonding, or otherwise.

Preferred compounds of the present invention include those in which, independently or in any combination:

R^1 is lower alkyl, particularly methyl or ethyl;

R^2 is a haloalkoxy or haloalkyl group;

R^3 is chlorine or bromine;

Y is chlorine or fluorine; and

R^4 is cyano, bromo, methoxy, nitro or methylsulphonyl.

Particularly favourable herbicidal properties are obtained in compounds in which R^2 is a halogen-substituted alkyl or alkoxy group. Halogen-substituted methyl, ethyl, methoxy and ethoxy groups appear to be most suitable and it is also preferred that there is more than one halogen substituent. Thus, examples of suitable R^2 substituents include di- and tri-halomethoxy and di- and tri- halomethyl groups with specific examples being dichloromethoxy, trifluoromethyl and, especially, difluoromethoxy.

Other particularly preferred compounds include those in which R^3 is chlorine and Y is fluorine.

Particular examples of compounds of the invention are listed in Table I in which, in all cases except for that of Compound 43, n is 0. For Compound 43, X is 5-chlorosulphonyl.

TABLE 1

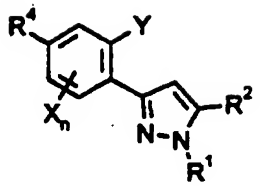
Comp. No.	R^1	R^2	R^3	R^4	Y
1	CH_3	$OCHF_2$	Cl	NO_2	F
2	CH_3	$OCHF_2$	Cl	NH_2	F
3	CH_3	$OCHF_2$	Cl	NO_2	Cl
4	CH_3	$OCHF_2$	Cl	NHCOMe	F
5	CH_3	$OCHF_2$	Cl	CO_2H	F
6	CH_3	$OCHF_2$	Cl	$NHCOCF_3$	F
7	CH_3	$OCHF_2$	Cl	SO_2Me	F
8	CH_3	$OCHF_2$	Cl	CO_2Me	F
9	CH_3	$OCHF_2$	Cl	SO_2Me	F
10	CH_3	$OCHF_2$	Cl	CO_2Et	F
11	CH_3	$OCHF_2$	Cl	$CONH_2$	F
12	CH_3	$OCHF_2$	Cl	Br	F
13	CH_3	$OCHF_2$	Cl	SCH_3	F
14	CH_3	$OCHF_2$	Cl	$NHSO_2Me$	F

Table I continued

Comp. No.	R^1	R^2	R^3	R^4	Y
15	CH_3	$OCHF_2$	Cl	OH	F
16	CH_3	$OCHF_2$	Cl	OCH_2CO_2Et	F
17	CH_3	$OCHF_2$	Cl	OSO_2CH_3	F
18	CH_3	$SCHF_2$	Cl	Cl	F
19	CH_3	$SOCHF_2$	Cl	Cl	F
20	CH_3	$OCHF_2$	Cl	$SOCH_3$	F
21	CH_3	$OCHF_2$	Cl	OCH_3	F
22	CH_3	$OCHF_2$	Cl	$OCHF_2$	F
23	CH_3	$SOCH_3$	Cl	Cl	F
24	CH_3	$OCHF_2$	Cl	CF_3	F
25	CH_3	$OCHF_2$	Br	CF_3	F
26	CH_3	$OCHF_2$	Cl	COCH	F
27	CH_3	$OCHF_2$	Cl	OCH_2CH_3	F
28	CH_3	$OCHF_2$	Cl	$OCH(CH_3)_2$	F
29	CH_3	$OCHF_2$	Cl	$O(CH_2)_2CH_3$	F
30	CH_3	$OCHF_2$	Cl	$O(CH_2)_3CH_3$	F
31	CH_3	$OCH_2CO_2CH_2CH_3$	Br	Cl	F
32	CH_3	$OCHF_2$	Cl	CH_3	F
33	CH_3	OCH_3	Cl	Cl	F
34	CH_3	Cl	Cl	Cl	F
35	CH_3	$OCHF_2$	Cl	$SOCH_2CH_3$	F
36	CH_3	$OCHF_2$	Cl	$SO(CH_2)_2CH_3$	F
38	CH_3	$OCHF_2$	Cl	$S(CH_2)_2CH_3$	F
39	CH_3	$OCHF_2$	Br	C≡CH	F
40	CH_3	$OCHF_2$	Cl	$CH=CH_2$	F
41	CH_3	$OCHF_2$	Br	NO_2	F
42	CH_3	$OCHF_2$	Cl	F	OCH_3
43	CH_3	$OCHF_2$	Cl	Cl	F
44	CH_3	$OCHF_2$	SO_2F	Cl	OCH_3
45	CH_3	$OCHF_2$	Cl	SO_2F	F
46	CH_3	$OCHF_2$	$CO_2CH_2CH_3$	Cl	F

Compounds of formula (I) may be prepared by similar routes to those set out in J03072460.

In particular, compounds of formula (I) in which R^3 is halogen may be prepared by halogenation of compounds of formula (II):



II

in which R^1, R^2, R^4, X, Y and n are as defined in relation to formula (I). This may be done using conventional techniques as described in the prior art. In particular the reaction may be effected in a solvent such as a halogenated hydrocarbon (for example dichloromethane, chloroform or carbon tetrachloride); an aromatic hydrocarbon (such as benzene, toluene or xylene); an ester such as ethyl acetate; a nitrile such as acetonitrile or benzonitrile; a chain-like ether such as diethyl ether or methylcellosolve; a cyclic ether such as dioxane and tetrahydrofuran; dimethylsulphoxide or dimethylformamide.

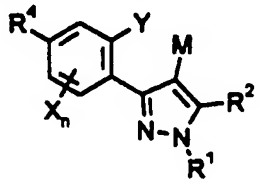
These solvents may be used individually, or they can be used in the form of mixtures.

A particularly preferred solvent is acetonitrile.

Suitable halogenating agents include chlorinating agents such as chlorine, phosphorus trichloride, phosphorus pentachloride and sulphuryl chloride, as well as other halogenating agents such as bromine and iodine.

The reaction temperature should be selected in the range from -30°C to 150°C, preferably from 10°C to 25°C which may be maintained by either the controlled addition of the chlorinating agent or cooling or both.

Compounds of general formula (I) in which R^3 is other than halogen may be synthesised from compounds of general formula (I) in which R^3 is halogen, especially bromine. For example, Compounds of general formula (I) in which R^3 is SO_2Z may be prepared from compounds of general formula (I) in which R^3 is bromine in a three step procedure as follows. Firstly, the compound of general formula (I) in which R^3 is halogen is converted to a compound of general formula (XXI):



XXI

wherein R^1, R^2, R^4, Y, X and n are as defined in general formula (I) and M is a metal, typically an alkali metal such as lithium or an alkaline earth metal halide such as a magnesium halide. When M is a metal, this conversion may be achieved by a transmetallation reaction with a compound of general formula (XXII):

$$R^{13}M$$

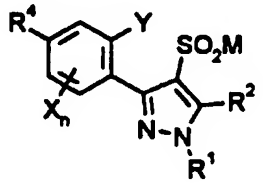
(XXII)

in which R^{13} is an optionally substituted alkyl, alkenyl, alkynyl or aryl group, preferably a lower alkyl such as n-butyl, and M is a metal, typically an alkali metal such as lithium.

The transmetallation reaction may be conducted in an aprotic solvent, for example an ether such as diethyl ether or tetrahydrofuran, typically under dry inert conditions such as a nitrogen or argon atmosphere. The reaction temperature may be between -100°C and 100°C, more usually between -90°C and 0°C.

Compounds of general formula (XXI) as defined above in which M is a metal halide, particularly a magnesium halide, may be prepared by the reaction of compounds of general formula (I) in which R^3 is bromine with magnesium in a dry aprotic solvent, for example an ether such as tetrahydrofuran or 1,2-dimethoxyethane. The reaction may be conducted at a temperature of between about 0°C and 200°C, usually between about 15°C and 100°C. It is often advantageous to carry out this reaction under an inert atmosphere such as nitrogen or argon and, under some circumstances, the reaction may be assisted by the presence of a catalytic amount of iodine or by the use of ultrasound.

The compound of general formula (XXI) may be reacted *in situ* with sulphur dioxide to give a compound of general formula (XXIII):



XXIII

wherein R^1, R^2, R^4, Y, X and n are as defined in general formula (I) and M is as defined for general formula (XXI).

If the compound of general formula (XXI) is not isolated before the reaction with sulphur dioxide then the reaction solvent will, of course, be the same solvent as was used for

the transmetallation reaction. The reaction is preferably carried out under similar conditions to the transmetallation reaction.

The compound of general formula (XXIII) may be converted to a compound of general formula (I) in which R^3 is SO_2Z and Z is chloro by reaction with a chlorinating agent such as thionyl chloride, sulphuryl chloride or oxalyl chloride. This chlorination reaction may be conducted in an inert solvent, typically an ether such as diethyl ether, a chlorinated solvent such as dichloromethane, an aromatic solvent such as 1,2-dichlorobenzene or a nitrile such as acetonitrile. It is preferable to carry out the reaction under a dry inert atmosphere such as nitrogen or argon and at a temperature of from -50°C to 200°C, more usually between 0°C and 100°C.

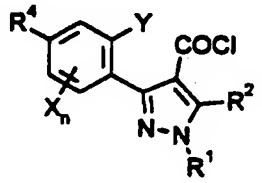
Compounds of formula (I) in which R^3 is SO_2Z and Z is other than chloro may be prepared from similar compounds in which Z is chloro by a halogen exchange reaction. In such a reaction, the starting material may be dissolved in a water miscible solvent, for example an ether such as tetrahydrofuran or 1,4-dioxane and then reacted with an aqueous solution of an inorganic or organic halide salt. Examples of suitable halide salts include alkali or alkaline earth metal halides such as potassium fluoride. The halogen exchange reaction may take place at a temperature of from 0°C to 200°C, for example from about 50°C to 150°C. In some cases, it is preferable also to conduct the reaction under an inert atmosphere such as nitrogen or argon.

Alternatively, the halogen exchange may be achieved by dissolving the compound of general formula (I) in which R^3 is SO_2Z in a water immiscible solvent, for example a haloalkane such as dichloromethane, an aromatic solvent such as 1,2-dichlorobenzene or an ether such as diethyl ether, and reacting the solution with a halide salt which may, but will not necessarily, be in aqueous solution. Typical inorganic halide salts are as mentioned above and include, for example, potassium fluoride. The reaction takes place in the presence of a phase transfer catalyst such as a tetraalkyl ammonium or tetraalkyl phosphonium salt, for example tetra-n-butylammonium bromide, or a crown ether and may be conducted at a temperature of from about -50°C to 200°C, usually from about 0°C to 150°C. In some cases, it is preferable to conduct the reaction under an inert atmosphere such as nitrogen or argon.

Compounds of general formula (I) in which R^3 is CO_2H may also be prepared from compounds of general formula (I) in which R^3 is halogen *via* compounds of general formula

(XXI) as defined above. The compound of general formula (XXI) is reacted with powdered solid carbon dioxide and then the reaction mixture is neutralised with an acid solution. Suitable acid solutions include aqueous solutions of mineral acids, for example dilute hydrochloric acid, or, alternatively, aqueous solutions of salts of weak bases, for example aqueous ammonium chloride. The reaction may be conducted at a temperature of from -80°C to 50°C, typically -10°C to 30°C.

Compounds of general formula (I) in which R^3 is CO_2H may be converted into compounds in which R^3 is CO_2R^5 and R^5 is other than H. One method of achieving this conversion is *via* a compound of general formula (XXIV):



XXIV

wherein R^1, R^2, R^4, Y, X and n are as defined in general formula (I).

Compounds of general formula (XXIV) may be synthesised from compounds of general formula (I) in which R^3 is CO_2H by chorination using an agent such as thionyl chloride or oxalyl chloride. The reaction may be carried out in the presence of a base, typically an inorganic base and in an inert solvent or mixture of solvents. Suitable solvents include chlorinated solvents such as dichloromethane; ethers such as diethyl ether; aromatic solvents such as 1,2-dichlorobenzene; and amides such as dimethylformamide. The reaction will generally be from -20°C to 150°C, more usually from 10°C to 80°C.

The compound of general formula (XXIV) may then be reacted with an alcohol of general formula (XIV):

R^5OH

XIV

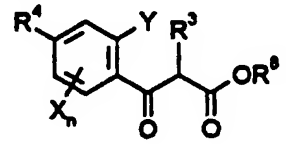
where R^5 is as defined for general formula (I) except that it is not hydrogen to give the required compound of general formula (I) in which R^3 is CO_2R^5 and R^5 is other than H. The reaction may be carried out in the presence of a base, which may be an inorganic base such as an alkali or alkaline earth metal hydroxide or carbonate, typically potassium carbonate, or an organic base such as a tertiary amine (for example triethylamine), an optionally substituted pyridine or a salt of an appropriate alkoxide. For example, when R^5 is ethyl, sodium ethoxide

may be used. The reaction may be carried out in an inert solvent, for example a halogenated solvent such as dichloromethane or an aromatic or heterocyclic solvent such as 1,2-dichlorobenzene or pyridine. A nucleophilic catalyst, for example a substituted pyridine, typically 4-N,N-dimethylaminopyridine may be employed and the reaction may be conducted at a temperature of from 0°C to 100°C, typically from 10°C to 40°C in an inert atmosphere.

An alternative synthesis for compounds of general formula (I) in which R^3 is CO_2R^5 and R^5 is other than H, is by the reaction of compounds of general formula (I) in which R^3 is CO_2H with compounds of formula (XIV) in the presence of a dehydrating agent such as a carbodiimide, typically N,N-dicyclohexylcarbodiimide, or a di-substituted carbonyl derivative of formula COQQ' where Q and Q' are leaving groups such as in 1,1-carbonyldiimidazole. A nucleophilic catalyst may also be present and the reaction should preferably be conducted in a dry inert atmosphere and in a solvent such as a halogenated solvent, for example dichloromethane; an ether, for example tetrahydrofuran; a nitrile, for example acetonitrile; an aromatic solvent, for example dichlorobenzene; or a heterocyclic solvent, for example pyridine. A base may also be present and suitable bases are inorganic bases such as alkali and alkaline earth metal hydroxides or carbonates, typically potassium carbonate. Alternatively, an organic base may be used and suitable examples include tertiary amines such as triethylamine or heterocyclic bases such as pyridine.

If the base is inorganic and is insoluble under the reaction conditions, a phase transfer catalyst may also be used. Suitable phase transfer catalysts include quaternary ammonium salts, for example tetrabutylammonium iodide, quaternary phosphonium salts, such as tetrabutyl phosphonium bromide, and crown ethers, for example 18-crown-6.

Compounds of general formula (I) in which R^2 is OH and R^3 is optionally substituted alkyl, alkenyl or alkynyl may be synthesised from compounds of general formula (IVa)



IVa

wherein R^4, X, Y and n are as defined in general formula (I), R^8 is as defined in general formula (IV) and R^3 is optionally substituted alkyl, alkenyl or alkynyl.

Compounds of general formula (IVa) may be prepared from compounds of general formula (IV) with an alkylating agent of formula:

R^3U

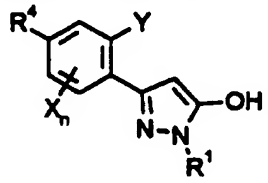
wherein R^3 is as optionally substituted alkyl, alkenyl or alkynyl and U is a leaving group, for example a halogen, particularly chlorine or iodine, a sulphonate ester such as tosylate, mesylate or triflate, or a sulphate half ester, particularly a dialkylsulphate such as dimethylsulphate.

The reaction should be conducted in the presence of a base, typically an alkali or alkaline earth metal carbonate, hydroxide or alkoxide although organic bases may also be used. Solvents suitable for this reaction include ethers such as tetrahydrofuran, amides such as N,N-dimethylformamide, nitriles such as acetonitrile, alcohols such as ethanol, esters such as ethyl acetate or other solvents such as dimethyl sulphoxide.

It is also possible to carry out the alkylation using an organometallic reagent of general formula (XXII) as defined above. Similar conditions may be used for this alkylation to those described for the synthesis of a compound of general formula (XXI).

Compounds of general formula (I) in which R^2 is OH can be converted to other compounds of general formula (I) using, for example the methods described for the preparation of compounds of general formula (II) in which R^2 is OR^5.

Compounds of formula (II) in which R^2 is OR^5 (except when R^5 is H), $O(alkyl)CO_2R^5$ or $O(alkyl)COR^5$ may be prepared from compounds of formula (III):



III

in which R^1, R^4, X, Y and n are as defined in relation to formula (I), by reaction with compounds of formula (R^cZ), where R^c is R^5 (except when R^5 is H), $(alkyl)CO_2R^5$ or $(alkyl)COR^5$ and Z is a leaving group, in the presence of a base as described in the art. Examples of suitable leaving groups include chlorine. A particularly preferred compound of formula (R^cZ) is chlorodifluoromethane.

The reaction is suitably effected in the presence of a solvent or mixtures of solvents, in the presence or absence of a base and optionally in the presence of a catalyst at a temperature between -10 and 100°C.

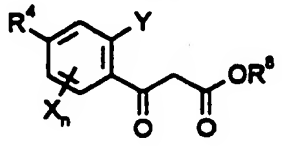
The applicants have found that this reaction is preferably undertaken as a stirred biphasic phase transfer reaction in the presence of an organic solvent and aqueous base solution in the presence of a phase transfer catalyst, preferably at room temperature. Suitable organic solvents are not miscible with water and include chlorinated solvents, for example, dichloromethane, aromatic solvents, for example, toluene, ethers, for example, diethyl ether and esters, for example, ethyl acetate. Dichloromethane is a preferred solvent.

Suitable phase transfer catalysts include tetraalkylammonium or tetraalklylphosphonium, salts, in particular tetrabutylphosphonium bromide. Suitable bases are water soluble and include, but are not limited to, alkali and alkaline earth carbonates, bicarbonates and hydroxides, for example, sodium hydroxide.

In particular, the compound of formula (III) is dissolved in an organic solvent such as dichloromethane with the phase transfer catalyst and the solution is saturated with the compound of formula (R^cZ), usually by bubbling this compound in the form of a gas through the solution. The reaction is then initiated by the addition of an aqueous solution of base such as a 50% solution of aqueous sodium hydroxide and the mixture stirred vigorously at room temperature.

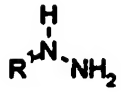
Compounds of general formula (II) in which R^2 is chloro may be synthesised from compounds of general formula (II) in which R^2 is OH by reaction with a chlorinating agent such as phosphorus oxytrichloride. The reaction may be carried out with or without a solvent and at a temperature of from 0°C to 200°C, preferably 20°C to 150°C.

Compounds of formula (III) may be prepared from compounds of formula (IV):



IV

in which R^4, X, Y and n are as defined in relation to formula (I) and R^8 is lower alkyl (preferably ethyl), by reaction with compounds of formula (V):

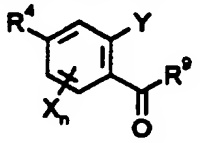


V

where R^1 is as defined in relation to formula (I). The reaction is carried out in the presence or absence of solvent, and optionally in the presence of a catalyst at temperatures of from -10°C to 150°C, in particular at the reflux temperature of any solvent present. Suitable solvents are those which dissolve both reactants and include alcohols, in particular the alcohol corresponding to the group R^8 in the compound of formula (IV). For instance, when R^8 is ethyl, a preferred solvent would be ethanol.

The applicants have found that the reaction may be carried out in the absence of any solvent. Thus the compound of formula (IV) is reacted directly with a appropriate alkylhydrazine, such as methylhydrazine, at elevated temperature, for example at about 70°C.

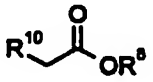
Compounds of formula (IV), where R^4, X, Y and n are as defined in relation to formula (I) and R^8 is lower alkyl, may be prepared from compounds of general formula (VI):



VI

wherein R^4, X, Y and n are defined in relation to formula (I) and R^9 is hydrogen, lower alkyl, hydroxy or a leaving group, for example halo such as chloro.

When R^9 is OH or a leaving group, the compound of general formula (VI) may be reacted with a compound of formula (VII):



VII

where R^8 is as defined above, and R^{10} is an activating group, or R^8 and R^{10} together form a cyclic activating group.

As used herein, the term "activating group" in compounds of formula (VII) means a group which increases the acidity of the hydrogen atoms on the adjacent carbon and is removable by acid catalysed hydroysis, or by base catalysed hydrolysis, or by alcholysis.

Examples of activating groups R^{10} include carboxylic ester groups, in particular alkyl ester groups, salts of carboxylate groups, nitriles and optionally N-substituted amides. In

particular R^{10} is either a carboxylate ester of formula CO_2R^{11} or a carboxylate salt of formula $CO_2^-R^{12+}$. Suitable groups R^{11} are optionally substituted alkyl groups such as ethyl, or R^{11} together with R^8 may be joined to form a cyclic structure. Suitable cations for R^{12+} are organic or inorganic cations. Preferably R^{12+} is an inorganic cation such as an alkali metal cation, suitably potassium. Compounds of formula (VII) are readily available or may be synthesised by methods known in the art. Particularly preferred compounds of formula (VII) are malonate half ester salts where R^8 is lower alkyl in particular ethyl and R^{10} is a group $CO_2^-R^{12+}$ where R^{12+} is an inorganic cation, in particular potassium.

Examples of cyclic activating groups include compounds where R^{10} is a group of formula CO_2R^{11} and R^{11} with R^8 together form a group $>C(CH_3)_2$. In this case, the compound of formula (VII) is Meldrum's acid.

The reaction may be carried out in the presence of solvents or mixtures of solvents. Suitable solvents include chlorinated solvents such as dichloromethane, aromatic solvents such as toluene, ether solvents such as diethyl ether and tetrahydrofuran and nitriles such as acetonitrile. Preferred solvents are acetonitrile and ethyl acetate.

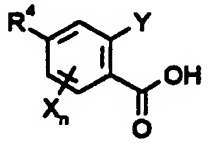
Furthermore, the reaction is carried out optionally in the presence of a base, and in the presence of a nucleophilic catalyst. An inert atmosphere such as nitrogen or argon may be employed. Temperatures of from -70° to 200°C, preferably from -10° to 100°C, and most preferably from 0° to 100°C, are suitably employed. The reaction conditions which give optimal results will vary depending upon the specific nature of the compounds of formulae (VI) and (VII). However the skilled chemist would be able to determine these readily.

Suitable bases for use in the reaction include inorganic bases such as alkali or alkaline earth metal hydroxides, bicarbonates, carbonates, hydrides or alcholates, in particular potassium carbonate, sodium hydroxide or sodium ethoxide. Alternatively organic bases such as tertiary amines, pyridine, substituted pyridines, Hunig's base and diazobicycloundecane may be used.

Suitable nucleophilic catalysts include pyridine, substituted pyridine, for example 4-N,N-dimethylaminopyridine, tertiary amines such as trialkylamines, N-hydroxysuccinimide and optionally substituted imidazoles.

The reaction may also require the presence of a non basic inorganic salt. Suitable salts include, but are not limited to, magnesium salts, in particular magnesium halides such as magnesium chloride.

When R^9 is hydroxy, i.e. the compound of formula (VI) is a compound of formula (VIII):



VIII

the compound of formula (IV) is preferably prepared using a base-mediated reaction as described above but additionally in the presence of a dehydrating agent such as carbonyldiimidazole or a carbodiimide, for example N,N'-dicyclohexylcarbodiimide. In this reaction, preferred temperatures are from -60° to 150°C, typically from 20° to 40°C; a preferred solvent is dichloromethane and a preferred base is triethylamine. 4-N,N-Dimethylaminopyidine is a typical nucleophilic catalyst for this reaction.

When the compound of formula (VII) is Meldrum's acid, the reaction is suitably effected in the presence of a base and in particular Hunig's base. Temperatures of from -60° to 100°C and in particular about 0°C are preferred in these circumstances, and dichloromethane is a preferred solvent.

When the compound of formula (VII) is a malonate half ester salt, such as potassium ethyl malonate, Compound (VI) is typically an acid chloride (i.e. R^9 is chloride).

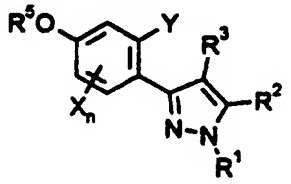
A typical process comprises the pre-formation of a slurry of the malonate half ester salt, a magnesium salt, preferably magnesium chloride, and a base, preferably triethylamine. The process is effected in an inert solvent, preferably acetonitrile, under an inert atmosphere of, for example, nitrogen, with vigorous stirring and cooling, typically to about 10°C. The reaction is typically initiated by the careful addition of the compound of formula (VI) where R^9 is chloro to the cooled reaction mixture, usually at about 0°C. The mixture is then stirred at a temperature between 0°C to 100°C, generally at room temperature, for an extended period, conveniently overnight.

Other compounds of formula VI in which R^4, Y, X and n are as defined in formula (I) and R^9 is hydrogen, halogen, hydroxy or lower alkyl, particularly methyl, may also be prepared by standard literature procedures.

Compounds of general formula (VIII) are readily available or may be prepared from readily available starting materials by standard procedures which would be familar to those skilled in the art.

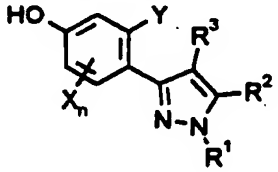
Many of the compounds of general formula (I) are easily synthesised from compounds of general formula (II) and such compounds include those in which R^4 is hydrogen, cyano, nitro, halogen, or optionally substituted alkyl, alkenyl or alkynyl. However, some compounds with more reactive R^4 groups are more suitably synthesised from other compounds of general formula (I), particularly those having the R^4 substituents just mentioned.

Thus, compounds of general formula (Ia):



Ia

where R^4 is OR^5 and R^5 is an alkyl, alkenyl or alkynyl group (any of which may optionally be substituted) may be synthesised from compounds of general formula (Ib):



Ib

in which R^4 is OH, by reaction with an alkylating agent of general formula (IX):

$$R^5\text{-}U$$

IX

wherein R^5 is as defined in general formula (Ia) and U is a leaving group. Examples of suitable leaving groups include halogen, such as chlorine or iodine, sulphonate esters such as tosylate, mesylate and triflate, and sulphate half esters, particularly as in dialkylsulphates such as dimethylsulphate.

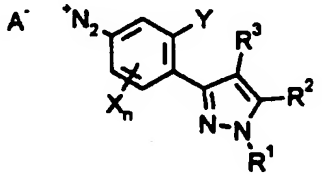
The reaction will usually be carried out in a solvent and suitable solvents include ketones, especially dialkyl ketones such as acetone; ethers such as diethyl ether; chlorinated alkyanes such as chloromethane; nitriles such as acetonitrile; amides such as dimethylformamide and aromatic solvents such as 1,2-dichlorobenzene.

It is often advantageous to include a base in the reaction mixture and suitable bases include inorganic bases such as alkali or alkaline earth metal hydroxides, hydrides or carbonates. Specific examples of such bases include potassium carbonate, sodium hydride and potassium hydroxide. Alternatively, an organic base, for example a tertiary amine such as triethylamine or a heterocyclic base such as pyridine may be used.

In order to optimise the reaction, it may be necessary to use a catalyst such as an iodide salt, for example potassium iodide. For a heterogenous reaction mixture a phase transfer catalyst may be preferred and examples of such catalysts include quaternary ammonium salts such as tetra n-butyl ammonium bromide, quaternary phosphonium salts such as tetra n-butyl phosphonium bromide and crown ethers such as 18-crown-6.

A suitable reaction temperature is from -30°C to 200°C, more usually from 0°C to 100°C. It may also be preferable to conduct this reaction in an inert atmosphere such as nitrogen or argon.

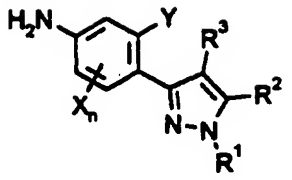
Compounds of general formula (Ib) may be prepared from diazonium salts of general formula (X):



X

wherein R^1, R^2, R^3, Y, X and n are as defined in general formula (I) and A^- is a suitable counter ion, typically tetrafluoroborate or halide, especially chloride, by reaction with an aqueous solution or suspension of an inorganic salt . Suitable inorganic salts are, for example, copper salts and typically a mixture of such salts is used. For example, cuprous oxide may be mixed with cupric nitrate. Typically, the reaction will be carried out at a temperature of 5°C to 30°C and cooling may be required to control the reaction.

Compounds of general formula (X) may be prepared from compounds of general formula (Ic):



Ic

where R^4 is NH_2, by diazotisation of the amino group. The reaction may be carried out using standard literature procedures, for example, the reaction of the compound of the formula (Ic) with an inorganic nitrite or an organic nitrite of general formula (XII):

$$R^{11}\text{-ONO}$$

XII

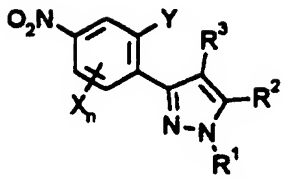
wherein R^{11} is typically an alkyl group.

When an inorganic nitrite is used in the reaction, the reaction may be carried out in aqueous solution in the presence of an acid such as hydrochloric acid, at a reaction temperature of from 0°C to 10°C, preferably 0°C. The inorganic nitrite will preferably be an alkali metal nitrite such as sodium nitrite. The product of general formula (X) may be used without further isolation or may be purified before further reaction.

When an organic nitrite of formula (XII), in which R^{11} is an alkyl residue, typically tert-butyl, is used, a compound of formula (Ic) is reacted with the nitrite of formula (XII) in an inert solvent. Suitable solvents include chlorinated alkanes, for example dichloroethane, and aromatics, for example 1,2-dichlorobenzene. Warming may be required to initiate the reaction and the reaction temperature is typically copntrolled by the rate of addition of a solution of Compound (XII) and a solution of Compound (Ic).

Suitable temperatures for the reaction are from -30°C to 200°C, typically 20°C to 70°C. Usually the compound of formula (X) formed in this reaction is reacted *in situ* with an appropriate reagent to form the desired compound of formula (I), for example a compound of formula (If) or (Iq) which have the structures given below.

Compounds of general (Ic) in which R^4 is NH_2 may be prepared from compounds of general formula (Id):



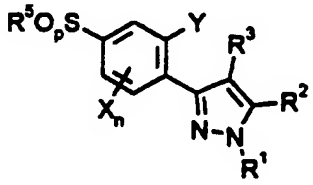
Id

in which R^4 is NO_2, by reduction. Methods for the reduction of nitro compounds to give amines are well known in the literature and, for example, the compound of general formula (Id) may be reduced using a transition metal salt such as titanium trichloride, usually in a solvent, for example a ketonic solvent such as acetone. Generally, such a reaction will be carried out between 0°C and 100°C, more typically, between 10°C and 40°C. An alternative reduction method uses a dissolving metal such as tin or zinc in an acid. Usually, the acid will be a mineral acid, such as aqueous hydrochloric acid, and a co-solvent, for example an alcohol such as methanol, may also be used. The reaction temperature will generally be between 0°C and 100°C and, preferably, will be between 10°C and 50°C.

Yet another method for the reduction of the nitro compounds (Id) is the use of a catalytic hydrogenation reaction which may be carried out at a pressure equal to or greater than one atmosphere and at a temperature of from 0°C to 200°C typically from 10 °C to 50°C. The reaction will generally be carried out in an alcoholic solvent such as ethanol or methanol in the presence of a transition metal catalyst such as palladium or platinum or one of their oxides, which may be on inert support such as charcoal.

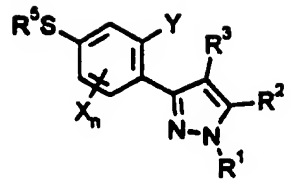
As already discussed, compounds of general formula (Id) can easily be synthesised from compounds of general formula (II) by the methods described above.

Compounds of general formula (Ie):



Ie

in which R^4 is SO_pR^5 may be prepared by the oxidation of the compounds of general formula (If):



(If)

in which R^4 is SR^5. Suitable oxidising agents for this conversion include peracids such as n-chloroperbenzoic acid, dioxiranes such as dimethyldioxirane, periodate salts such as potassium periodate and salts of higher oxidation states transition metals including potassium permanganate. The reaction will usually be carried out in a solvent such as a ketone, for example acetone; a chlorinated alkane such as dichloromethane or chloroform; an ether such as tetrahydrofuran; an aromatic solvent such as 1,2-dichlorobenzene or a heterocyclic solvent such as pyridine. The reaction may be conducted at a temperature of from -30°C to 200°C, typically from 0°C to 40°C. It is generally preferable for the reaction to be carried out in an inert atmosphere such as argon or nitrogen.

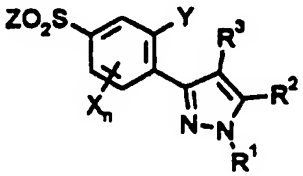
Compounds of general formula (If) may be prepared from compounds of general formula (X) by reaction with a compound of general formula (XI):

$$R^5S\text{-}SR^5$$

XI

in which R^5 is as defined for general formula (I). The reaction may be carried out under an inert atmosphere such as nitrogen or argon at a temperature of from -30°C to 100°C, typically 0°C to 70°C. Suitable solvents include halogenated alkanes such as 1,2-dichloroethane or dichloromethane; ethers such as diethyl ether and tetrahydrofuran; and aromatic solvents such as 1,2-dichlorobenzene. Compounds of general formula (X) may be prepared as specified above.

Compounds of general formula (Iq):

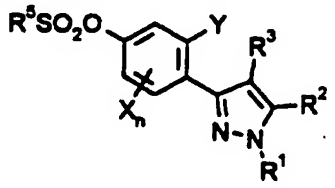


Iq

in which R^4 is SO_2Z and Z is halo, typically chloro or bromo may alos be prepared from compounds of general formula (X) by reaction with sulphur dioxide in the presence of an

inorganic salt or mixture of salts. Suitable inorganic salts include copper salts especially copper (I) salts such as copper (I) halides, in particular cuprous chloride. The sulphur dioxide will often be in solution with typical solvents being organic acids, espeically alkanoic acids such as acetic acid. A preferred experimental procedure involves saturating the solvent with sulphur dioxide piror to initiation of the reaciton with the compound of general formula (X). The addition of the sulphur dioxide to the compound of general formula (X) may take place at reduced temperature, for example about -40°C to 30°C, more usually from about -5°C to 15°C with the reaction mixture subsequently being allowed to warm to room temperature. The product of this reaction is a compound of general formula (Iq) in which R^4 is chloro. If compounds in which R^4 is halo other than chloro are required, these may be synthesised from compounds of general formula (Iq) in which R^4 is chloro by a halogen exchange reaction with an organic or inorganic halide salt, typically a salt such as potassium fluoride. The starting compound of general formula (I) may either be dissolved in a water miscible solvent such as 1,4-dioxane or tetrahydrofuran and reacted with an aqueous solution of the salt or it may be dissolved in a solvent such as dichloromethane which is not water miscible and reacted with the salt or an aqueous solution of the salt in the presence of a phase transfer catalyst. The halogen exchange reaction may take place at a temperature of from 0°C to 200°C, for example from about 50°C to 150°C. In some cases, it is preferable also to conduct the reaction under an inert atmosphere such as nitrogen or argon.

Compounds of general formula (Ig):



Ig

in which R^4 is R^5SO_2O- and R^5 is as defined in general formula (I) may be prepared by the reaction of a compound of general formula (Ib) with a sulphonyl chloride of general formula (XIII):

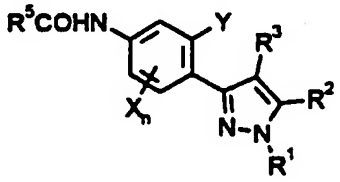
$$R^5SO_2Cl$$

XIII

where R^5 is as defined in general formula (I). The reaction may be carried out in a suitable solvent for example a halogenated alkane, such as dichloromethane; an ether such as

tetrahydrofuran; a nitrile such as acetonitrile; an amide such as dimethylformamide; an aromatic solvent such as 1,2-dichlorobenzene; or a heterocyclic solvent such as pyridine. Usually the reaction will be carried out in an inert atmosphere at a temperature of from -30°C to 100°C, typically from 0°C to 70°C. The reaction will usually be conducted in the presence of a base which may be an inorganic base such as an alkali or alkaline earth metal hydroxide or carbonate, typically potassium carbonate; or an organic base, suitably a tertiary amine such as triethylamine or a heterocyclic base such as pyridine or imidazole. A nucleophilic catalyst will often be required and suitable catalysts include heterocycles, for example a pyridine such as 4-N,N-dimethylaminopyridine or an imidazole. Most suitably, the reaction will be carried out under an inert atmosphere such as nitrogen or argon.

Compounds of general formula (Ih):

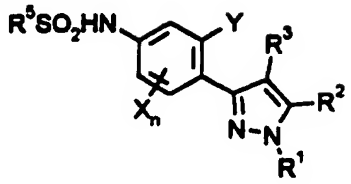


Ih

in which R^4 is $NHCOR^5$ and R^5 is as defined in general formula (I), may be prepared from a compound of general formula (Ic) by reaction with an acid chloride, an acid anhydride or an acid in the presence of a dehydrating agent such a carbodiimide, typically N,N'-dicyclohexylcarboiimide. Alternative dehydration agents include disubstituted carbonyl derivatives of formula COQQ', where Q and Q' are leaving groups, for example 1,1'-carbonyldiimidazole. Alternatively, the compound of general formula (Ic) may be reacted with a methyl ester in the presence of a trialkylaluminium species such as trimethylaluminium. In either case, the reaction will, in most cases, be carried out in the presence of a base which may be an inorganic base such as an alkali or alkine earth metal hydroxide, carbonate or bicarbonate, typically potassium carbonate; or an organic base, for an example a tertiary amine such as triethylamine. A heterocyclic base such as pyridine or imidazole may also be used.

A nucleophilic catalyst will often be required and suitable catalysts include heterocycles such as 4-N,N-dimethylaminopyridine or imidazole. The reaction may be carried out under an inert atmosphere such as nitrogen or argon at a temperature of -30°C to 200°C, more typically, 0°C to 100°C.

Compounds of general formula (Ii):

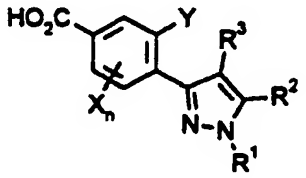


Ii

in which R^4 is $-NHSO_2R^5$ and R^5 is as described in formula (I), may also be prepared from compounds of general formula (Ic) by reaction with a sulphonyl chloride of general formula (XIII) in which R^5 is as defined in general formula (I). The reaction may be carried out in a solvent such as a halogenated alkane for example dichloromethane; an ether such as tetrahydrofuran; a nitrile such as acetonitrile; an amide such as dimethylformamide; an aromatic solvent such as 1,2-dichlorobenzene; a heterocyclic solvent such as pyridine; or a polar solvent such as dimethylsulphoxide. A nucleophilic catalyst such as those defined above may be used and the reaction will usually be carried out in an anhydrous inert atmosphere at a temperature of from -30°C to 200°C, typically from 0°C to 100°C. The reaction will usually be conducted in the presence of an organic or an inorganic base and, suitable bases are those listed above for the conversion of compound of general formula (Ic) to the compound of general formula (Ih).

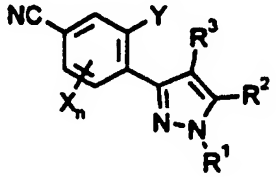
The synthesis of Compounds (Ia) to (Ii) and (Iq) is summarised in Reaction Scheme I.

Compounds of formula (II):



II

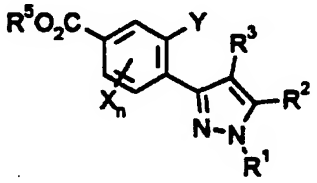
in which R^4 is CO_2R^5 and R^5 is hydrogen may be prepared by the hydrolysis of compounds of general formula (Im):



Im.

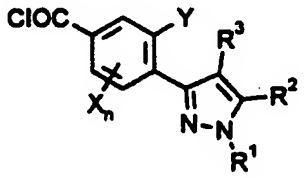
The hydrolysis may be either acid or base catalysed and may be carried out in either an aqueous or a non-aqueous medium. Generally an organic solvent will be used and the reaction temperature will be between 0°C and 200°C, typically 50°C to 120°C. Suitable acid catalysts include mineral acids such as hydrochloric or sulphuric acid and base catalysts include alkaline and alkaline earth metal hydroxides or carbonates, for example potassium hydroxide. The reaction solvent may be an alcohol such as ethanol; an ether such as tetrahydrofuran; or a nitrile such as acetonitrile; or water. A mixture of solvents may be used. In some circumstances, a phase transfer catalyst may be required and suitable agents include crown ethers, tetraalkylammonium salts or tetraalkylphosphonium salts.

Compounds of general formula (Ij):



Ij

in which R^4 is CO_2R^5 and R^5 is other than hydrogen, may be prepared from compounds general formula (XV):



XV

in which R^1, R^2, R^3, X, Y and n are as defined in general formula (I), by reaction with an alcohol of general formula (XIV):

R^5OH

XIV

where R^5 is as defined for general formula (I) except that it is not hydrogen. The reaction may be carried out in the presence of a base, which may be an inorganic base such as an alkali or alkaline earth metal hydroxide or carbonate, typically potassium carbonate, or an organic base such as a tertiary amine (for example triethylamine), an optionally substituted pyridine or a salt of an appropriate alkoxide. For example, when R^5 is ethyl, sodium ethoxide may be used. The reaction may be carried out in an inert solvent, for example a halogenated solvent

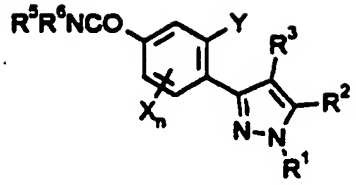
such as dichloromethane or an aromatic or heterocyclic solvent such as 1,2-dichlorobenzene or pyridine. A nucleophilic catalyst, for example a substituted pyridine, typically 4-N,N-dimethylaminopyridine may be employed and the reaction may be conducted at a temperature of from 0°C to 100°C, typically from 10°C to 40°C in an inert atmosphere.

Compounds of general formula (XV) may be synthesised from a compound of general formula (II) by chorination using an agent such as thionyl chloride or oxalyl chloride. The reaction may be carried out in the presence of a base, typically an inorganic base and in an inert solvent or mixture of solvents. Suitable solvents include chlorinated solvents such as dichloromethane; ethers such as diethyl ether; aromatic solvents such as 1,2-dichlorobenzene; and amides such as dimethylformamide. The reaction will generally be from -20°C to 150°C, more usually from 10°C to 80°C.

An alternative synthesis for compounds of general formula (Ij) is the reaction of compounds of (II) with compounds of formula (XIV) in the presence of a dehydrating agent such as a carbodiimide, typically N,N-dicyclohexylcarbodiimide, or a di-substituted carbonyl derivative of formula COQQ' where Q and Q' are leaving groups such as in 1,1-carbonyldiimidazole. A nucleophilic catalyst may also be present and the reaction should preferably be conducted in a dry inert atmosphere and in a solvent such as a halogenated solvent, for example dichloromethane; an ether, for example tetrahydrofuran; a nitrile, for example acetonitrile; an aromatic solvent, for example dichlorobenzene; or a heterocyclic solvent, for example pyridine. A base may also be present and suitable bases are inorganic bases such as alkali and alkaline earth metal hydroxides or carbonates, typically potassium carbonate. Alternatively, an organic base may be used and suitable examples include tertiary amines such as triethylamine or heterocyclic bases such as pyridine.

If the base is inorganic and is insoluble under the reaction conditions, a phase transfer catalyst may also be used. Suitable phase transfer catalysts include quaternary ammonium salts, for example tetrabutylammonium iodide, quaternary phosphonium salts, such as tetrabutyl phosphonium bromide, and crown ethers, for example 18-crown-6.

Compounds of general formula (Ik):



Ik

in which R^4 is $CONR^5R^6$ may also be prepared from compound (II) or compound (XV) by reaction with a compound of general formula XVI:

R^5R^6NH

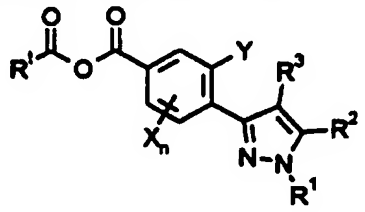
XVI

in which R^5 and R^6 are as defined in general formula (I). The reaction may be carried out in the presence of a base which may be either organic or inorganic. Suitable inorganic bases include alkali or alkaline earth metal carbonates and bicarbonates, for example potassium carbonate; and organic bases include tertiary amines, for example triethylamine, and pyridine. Suitable solvents for the reaction include chlorinated solvents such as dichloromethane; ethers such as tetrahydrofuran; nitriles such as acetonitrile; and amides such as dimethylformamide. A mixture of solvents may also be employed and, in some cases, the mixture may be heterogenous with organic and aqueous phases. It is often preferable to employ a nucleophilic catalyst such as 4-N,N-dimethylaminopyridine, pyridine or imidazole. The reaction may be carried out in an inert atmosphere at a temperature of -20°C to 150°C, typically 10°C-80°C. When the compounds of general formula (Ik) are prepared from the compound of general formula (II), it may be necessary to include a dehydrating agent such as N,N'-dicyclohexylcarbodiimide or a di-substituted carbonyl derivative of general formula QCOQ', where Q and Q' are leaving groups which may be the same or different. Examples of such disubstituted carbonyl derivatives include 1,1-carbonyldiimidazole.

An alternative route for the production of compounds of general formula (Ik) is by the reaction of compounds (Im), in which R^4 is nitrile, by controlled hydrolysis. This is appropriate for compounds of general formula (Ik) in which R^5 and R^6 are both hydrogen. The reaction may be carried out under either acidic or basic conditions, optionally in an aqueous solvent. The reaction temperature will generally be between 0°C and 200°C, more typically between 50°C and 120°C. Suitable acids are hydrochloric acid and sulphuric acid while for base catalysed reactions, suitable bases include alkali and alkaline earth metal

hydroxides and carbonates. Suitable solvents for the reaction include ethers such as tetrahydrofuran, nitriles such as acetonitrile, amides such as N,N-dimethylformamide, water and mixtures of these.

Yet a further method for the preparation of a compound of general formula (Ik) is by the reaction of a compound of general formula (XVIII):



XVIII

wherein R^1, R^2, R^3, Y, X and n are as defined in general formula I and R^t is an alkyl group, for example a tertiary alkyl group such as tertiary butyl, with an amine of general formula (XVI). The reaction may be carried out in the presence of a nucleophilic catalyst in an inert atmosphere at a temperature of -20°C to 200°C, more typically from 0°C to 100°C. Suitable reaction solvents include chlorinated aliphatic solvents such as dichloromethane; ethers such as tetrahydrofuran; aromatic solvents such as 1,2-dichlorobenzene; nitriles such as acetonitrile; amides such as dimethylformamide; and heterocyclic solvents such as pyridine. Suitable nucleophilic catalysts include pyridines, such as 4-N,N-dimethylaminopyridine, and imidazoles.

Compounds of general formula (XVIII) can be prepared from compounds of general formula (II) by reaction with compounds of general formula (XVII):

R^t-COCl

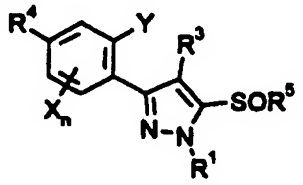
XVII

in which R^t is an alkyl, typically a tertiary alkyl, group for example tertiary butyl.

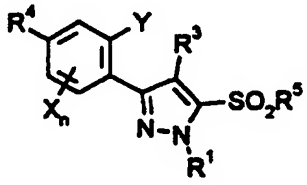
The reaction may be carried out in the presence of a base and/or a nucleophilic catalyst. In some circumstances, it may be preferable to employ an anhydrous inert atmosphere such as nitrogen or argon and the temperature may be from -20°C to 200°C, typically from 0°C to 100°C. The solvent may be a chlorinated alkane, an ether, a nitrile, an aromatic or heterocyclic solvent or an amide. The base may be either an inorganic or an organic base and the nucleophilic catalyst may be a heterocyclic catalyst such as a 4-N,N-dimethylaminopyridine or an imidazole.

In an alternative method, compounds of general (Ik) may be synthesised directly from compounds of general formula (Ij), wherein R^5 is alkyl, in particular methyl, by reaction with an amine of general formula (XVI). The reaction proceeds most favourably in the presence of a catalyst, particularly an aluminium based derivative. Examples of these include trialkyl aluminiums, and especially lower alkylaluminiums such as trimethylaluminium. Appropriate reaction solvents include fluorinated alkanes, ethers and aromatic solvents. The reaction is preferably carried out in an inert atomosphere at a temperature of from -20°C to 200°C, more typically from 0 °C to 50°C. The synthesis of Compounds (Ij), (Ik), (Il), and (Im) is summarised in Reaction Scheme II.

Compounds of general formula (I) in which R^2 is SO_mR^5 (wherein m and R^5 are defined above) are also not easily synthesised by the route shown above. Compounds of general formula (In) and (Io):

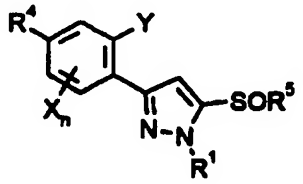


In

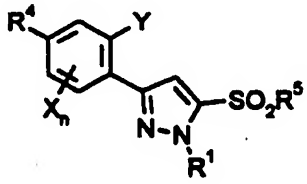


Io

wherein R^1, R^3, R^4, Y, X and n are as defined for general formula (I) and in which R^2 is SOR^5 and SO_2R^5 respectively (with R^5 as defined for general formula (I)) may be synthesised using previously defined methods from corresponding compounds of general formulae (IIn) and (IIo):



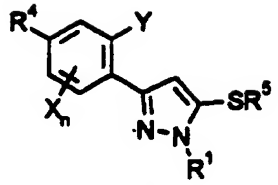
IIn



IIo

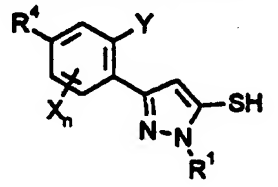
wherein R^1, R^3, R^4, R^5, Y, X and n are as defined for general formula (I).

Compounds of general formula (IIn) and (IIo) may be synthesised from compounds of general formula (IIa):



IIa

wherein R^2 is SR^5, by oxidation. Suitable oxidising agents include peracids, such as m-chloroperbenzoic acid; periodate salts such as potassium periodate; and salts of higher oxidation state transistion metals, for example potassium permanganate. The amount and type of oxidising agent used may be chosen by the chemist according to whether a compound of general formula (IIn) or (IIo) is required. The reaction may be carried out in an anhydrous inert atmosphere and an anhydrous solvent such as a halogenated alkane, ether or an aromatic solvent may be used. Specific solvents include chloromethane, chloroform, diethyl ether and 1,2-dichlorobenzene. Alternatively with some reagents, for example transition metal salts, aqueous media may be preferred. A mixture of solvents may also used. The reaction temperature will generally be between -20°C and 200°C, more suitably between 0°C and 100°C. Compounds of general formula (IIa) in which R^5 is other than hydrogen may be prepared as described above from compounds of general formula (IIb):

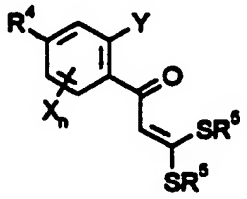


IIb

in which R^2 is SH using analagous methods to those described above for the synthesis of compounds of compounds of general formula II from compounds of general formula III.

Compounds of general formula (IIb) may be synthesised from compounds (III) using a suitable thionating agent such as Lawesson's reagent 2,4-bis(4-methyloxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide. The reaction may be conducted at a temperature of from -30°C to 200°C, usually from 50°C to 200°C. The reaction temperature will depend to a large extent on the solvent which is used and suitable solvents include chlorinated alkanes, ethers and aromatics. Specific examples of solvents are chloroform, tetrahydrofuran, xylene and 1,2-dichlorobenzene.

An alternative route for the synthesis of compounds of general formula (IIa) is by the reaction of general formula (XIX):



XIX

wherein R^4, R^5, Y, X and n are as defined for general formula (I), with a compound of general formula (V) under similar conditions to those employed in the conversion of compounds of general formula (IV) to compounds of general formula (III).

Compounds of general formula (XIX) may be prepared by the sequential reaction of a compound of general formula (VI) as defined above in which R^9 is lower alkyl, in particular methyl, with carbondisulphide and then an alkylating agent of general formula (IX):

R^5-U

IX

wherein R^5 is as defined in general formula (I) and U is a leaving group. Typical leaving groups, U, include halogen, particularly iodide, sulphonate esters such as tosylate and sulphate half esters as in, for example, dimethylsulphate. The reaction may be carried out in a solvent or a mixture of solvents and suitable solvents are chosen from aromatic solvents, amides, ethers and chlorinated alkanes. Specific examples of suitable solvents include toluene, dimethylacetamide, tetrahydrofuran and dichloromethane.

Generally, an organic or inorganic base will be present in the reaction mixture. Examples of inorganic bases include alkali or alkaline earth metal hydrides, hydroxides or carbonates typically sodium hydroxide. Examples of organic bases are alkali metal alkoxides, particularly sodium ethoxide, and tertiary amines such as diazobicycloundecane. The reaction temperature will typically be -30°C to 200°C , more probably from 0°C to 50°C.

The synthesis of compounds of general formula (XI) has already been described above.

The synthesis of compounds (In), (Io), (IIb), (IIn) and (IIo) is summarised in Reaction Scheme III.

The compounds of formula (I) above are active as herbicides and the invention therefore provides, in a further aspect, a process for severely damaging or killing unwanted

plants, which process comprises applying to the plants, or to the growth medium of the plants, a herbicidally effective amount of a compound of formula (I) as hereinbefore defined.

The compounds of formula (I) are active against a broad range of weed species including monocotyledonous and dicotyledonous species. They show some selectivity towards certain species; they may be used, for example, as selective herbicides in soya crops. The compounds of formula (I) may be applied directly to unwanted plants (post-emergence application) but they are preferably applied to the soil before the unwanted plants emerge (pre-emergence application).

The compounds of formula (I) may be used on their own to kill or severely damage plants, but are preferably used in the form of a composition comprising a compound of formula (I) in admixture with a carrier comprising a solid or liquid diluent.

Compositions containing compounds of formula (I) include both dilute compositions, which are ready for immediate use, and concentrated compositions, which require to be diluted before use, usually with water. Preferably the compositions contain from 0.01% to 90% by weight of the active ingredient. Dilute compositions ready for use preferably contain from 0.01 to 2% of active ingredient, while concentrated compositions may contain from 20 to 90% of active ingredient, although from 20 to 70% is usually preferred.

The solid compositions may be in the form of granules, or dusting powders wherein the active ingredient is mixed with a finely divided solid diluent, e.g. kaolin, bentonite, kieselguhr, dolomite, calcium carbonate, talc, powdered magnesia, Fuller's earth and gypsum. They may also be in the form of dispersible powders or grains, comprising a wetting agent to facilitate the dispersion of the powder or grains in liquid. Solid compositions in the form of a powder may be applied as foliar dusts.

Liquid compositions may comprise a solution or dispersion of an active ingredient in water optionally containing a surface-active agent, or may comprise a solution or dispersion of an active ingredient in a water-immiscible organic solvent which is dispersed as droplets in water.

Surface-active agents may be of the cationic, anionic, or non-ionic type or mixtures thereof. The cationic agents are, for example, quaternary ammonium compounds (e.g. cetyltrimethylammonium bromide). Suitable anionic agents are soaps; salts of aliphatic mono ester of sulphuric acid, for example sodium lauryl sulphate; and salts of sulphonated aromatic

compounds, for example sodium dodecylbenzenesulphonate, sodium,calcium, and ammonium lignosulphonate, butylnaphthalene sulphonate, and a mixture of the sodium salts of diisopropyl and triisopropylnaphthalenesulphonic acid. Suitable non-ionic agents are the condensation products of ethylene oxide with fatty alcohols such as oleyl alcohol and cetyl alcohol, or with alkylphenols such as octyl- or nonyl- phenol (e.g. Agral 90) or octyl-cresol. Other non-ionic agents are the partial esters derived from long chain fatty acids and hexitol anhydrides, for example sorbitan monolaurate; the condensation products of the partial ester with ethylene oxide; the lecithins; and silicone surface active agents (water soluble surface active agents having a skeleton which comprises a siloxane chain e.g. Silwet L77). A suitable mixture in mineral oil is Atplus 411F.

The aqueous solutions or dispersions may be prepared by dissolving the active ingredient in water or an organic solvent optionally containing wetting or dispersing agent(s) and then, when organic solvents are used, adding the mixture so obtained to water optionally containing wetting or dispersing agent(s). Suitable organic solvents include, for example, ethylene di-chloride, isopropyl alcohol, propylene glycol, diacetone alcohol, toluene, kerosene, methylnaphthalene, the xylenes and trichloroethylene.

The compositions for use in the form of aqueous solutions or dispersions are generally supplied in the form of a concentrate containing a high proportion of the active ingredient, and the concentrate is then diluted with water before use. The concentrates are usually required to withstand storage for prolonged periods and, after such storage, to be capable of dilution with water to form aqueous preparations which remain homogeneous for a sufficient time to enable them to be applied by conventional spray equipment. Concentrates conveniently contain 20-90%, preferably 20-70%, by weight of the active ingredient(s). Dilute preparations ready for use may contain varying amounts of the active ingredient(s) depending upon the intended purpose; amounts of 0.01% to 10.0% and preferably 0.1% to 2%, by weight of active ingredient(s) are normally used.

A preferred form of concentrated composition comprises the active ingredient which has been finely divided and which has been dispersed in water in the presence of a surface-active agent and a suspending agent. Suitable suspending agents are hydrophilic colloids and include, for example polyvinylpyrrolidone and sodium carboxymethylcellulose, and vegetable gums, for example gum acacia and gum tragacanth. Preferred suspending

agents are those which impart thixotropic properties to, and increase the viscosity of the concentrate. Examples of preferred suspending agents include hydrated colloidal mineral silicates, such as montmorillonite, beidellite, nontronite, hectorite, saponite, and saucorite. Bentonite is especially preferred. Other suspending agents include cellulose derivatives and polyvinyl alcohol.

The rate of application of the compounds of the invention will depend on a number of factors including, for example, the compound chosen for use, the identity of the plants whose growth is to be inhibited, the formulations selected for use and whether the compound is to be applied for foliage or root uptake. As a general guide, however, an application rate of from 0.001 to 20 kilograms per hectare is suitable while from 0.025 to 1 kilograms per hectare may be preferred.

The compositions of the invention may comprise, in addition to one or more compounds of the invention, one or more compounds not of the invention but which possess biological activity. Accordingly in yet a still further embodiment the invention provides a herbicidal composition comprising a mixture of at least one herbicidal compound of formula (I) as hereinbefore defined with at least one other herbicide.

The other herbicide may be any herbicide not having the formula (I). It will generally be a herbicide having a complementary action in the particular application.

Examples of useful complementary herbicides include:

A. benzo-2,1,3-thiadiazin-4-one-2,2-dioxides such as bentazone;

B. hormone herbicides, particularly the phenoxy alkanoic acids such as MCPA, MCPA-thioethyl, dichlorprop, 2,4,5-T, MCPB, 2,4-D, 2,4-DB, mecoprop, trichlopyr, clopyralid, and their derivatives (eg. salts, esters and amides);

C. 1,3 dimethylpyrazole derivatives such as pyrazoxyfen, pyrazolate and benzofenap;

D. Dinitrophenols and their derivatives (eg. acetates) such as dinoterb, dinoseb and its ester, dinoseb acetate;

E. dinitroaniline herbicides such as dinitramine, trifluralin, ethalflurolin, pendimethalin, oryzalin;

F. arylurea herbicides such as diuron, flumeturon, metoxuron, neburon, isoproturon, chlorotoluron, chloroxuron, linuron, monolinuron, chlorobromuron, daimuron, methabenzthiazuron;

G. phenylcarbamoyloxyphenylcarbamates such as phenmedipham and desmedipham;

H. 2-phenylpyridazin-3-ones such as chloridazon and norflurazon;

I. uracil herbicides such as lenacil, bromacil and terbacil;

J. triazine herbicides such as atrazine, simazine, aziprotryne, cyanazine, prometryn, dimethametryn, simetryne, and terbutryn;

K. phosphorothioate herbicides such as piperophos, bensulide, and butamifos;

L. thiolcarbamate herbicides such as cycloate, vernolate, molinate, thiobencarb, butylate*, EPTC*, tri-allate, di-allate, esprocarb, tiocarbazil, pyridate, and dimepiperate;

M. 1,2,4-triazin-5-one herbicides such as metamitron and metribuzin;

N. benzoic acid herbicides such as 2,3,6-TBA, dicamba and chloramben;

O. anilide herbicides such as pretilachlor, butachlor, alachlor, propachlor, propanil, metazachlor, metolachlor, acetochlor, and dimethachlor;

P. dihalobenzonitrile herbicides such as dichlobenil, bromoxynil and ioxynil;

Q. haloalkanoic herbicides such as dalapon, TCA and salts thereof;

R. diphenylether herbicides such as lactofen, fluroglycofen or salts or ester thereof, nitrofen, bifenox, aciflurofen and salts and esters thereof, oxyfluorfen, fomesafen, chlornitrofen and chlomethoxyfen;

S. phenoxyphenoxypropionate herbicides such as diclofop and esters thereof such as the methyl ester, fluazifop and esters thereof, haloxyfop and esters thereof, quizalofop and esters thereof and fenoxaprop and esters thereof such as the ethyl ester;

T. cyclohexanedione herbicides such as alloxydim and salts thereof, sethoxydim, cycloxydim, tralkoxydim, and clethodim;

U. sulfonyl urea herbicides such as chlorosulfuron, sulfometuron, metsulfuron and esters thereof; benzsulfuron and esters thereof such as DPX-M6313, chlorimuron and esters such as the ethyl ester thereof pirimisulfuron and esters

such as the methyl ester thereof, 2-[3-(4-methoxy-6-methyl-1,3,5-triazin-zyl)-3-methylureidosulphonyl) benzoic acid esters such as the methyl ester thereof (DPX-LS300) and pyrazosulfuron;

V. imidazolidinone herbicides such as imazaquin, imazamethabenz, imazapyr and isopropylammonium salts thereof, imazethapyr;

W. arylanilide herbicides such as flamprop and esters thereof, benzoylprop-ethyl, diflufenican;

X. amino acid herbicides such as glyphosate and glufosinate and their salts and esters, sulphosate and bialaphos;

Y. organoarsenical herbicides such as monosodium methanearsonate (MSMA);

Z. herbicidal amide derivative such as napropamide, propyzamide, carbetamide, tebutam, bromobutide, isoxaben, naproanilide and naptalam;

AA. miscellaneous herbicides including ethofumesate, cinmethylin, difenzoquat and salts thereof such as the methyl sulphate salt, clomazone, oxadiazon, bromofenoxim, barban, tridiphane, flurochloridone, quinchlorac, mefanacet, and triketone herbicides such as sulcotrione;

BB. Examples of useful contact herbicides include:

bipyridylium herbicides such as those in which the active entity is paraquat and those in which the active entity is diquat;

* These compounds are preferably employed in combination with a safener such as dichlormid.

The invention is illustrated by the following Examples. (The preparation of intermediates is described in the Preparative Examples). The abbreviations used in the Examples have the following meanings:

NMR spectrum: nuclear magnetic resonance spectrum which were recorded at 270 or 400 MHz. (This refers to the proton magnetic resonance spectrum unless otherwise stated). The following abbreviations are used to indicate the multiplicity of the peaks in the NMR spectrum: s (singlet); d (doublet); t (triplet); q (quartet) quin (quintet) m (multiplet; br (broad).

IR spectrum: infra-red absorption spectrum.

MS: mass spectrum GLC: gas liquid chromatography

GC: gas chromatography TLC: thin layer chromatography

m.p.: melting point b.p: boiling point

EXAMPLE 1

This example illustrates the preparation of Compound 1 in Table I.

Step a: Preparation of 2-fluoro-4-nitrobenzoylchloride.

A mixture of 2-fluoro-4-nitrobenzoic acid (10g) in thionyl chloride (100 ml) was heated at reflux for 3 hours. After cooling, the excess thionylchloride was removed under *vacuo* to give an orange brown oil (11.4g, 100%) which was used without further purification

Step b: Preparation of ethyl 3-(2-fluoro-4-nitrophenyl)-3-oxoproprionate.

Triethylamine (9.7g) and magnesium chloride (11.4g) were added with vigorous stirring to a mixture of potassium ethyl malonate (17.95g) in acetonitrile (75 ml) already cooled to less than 10°C under an inert atmosphere of nitrogen. The mixture was allowed to warm to room temperature and stirred for a further 2½ hours. The slurry was then cooled to 0°C and 2-fluoro-4-nitrobenzoylchloride (10g), prepared as described in Step a, in acetonitrile was added dropwise over 15 minutes. A further portion of triethylamine (0.97g) was added and the mixture allowed to warm to room temperature, then stirred overnight.

The reaction mixture was concentrated under *vacuo* to remove the acetonitrile, suspended in toluene and reconcentrated under *vacuo*. The residue was suspended in ethyl acetate and the mixture cooled to 10°C. Aqueous 13% hydrochloric acid (50 ml) was added carefully to the mixture with vigorous stirring while maintaining the temperature at less than 25°C. On completion of the addition of acid, the reaction mixture was allowed to stand and separated into two layers. The layers were separated and the aqueous phase was extracted with ethyl acetate. The organic phase and ethyl acetate extracts were combined, washed with 13% aqueous hydrochloric acid and water, dried over anhydrous magnesium sulphate and concentrated under *vacuo* to give a pale orange gum which solidified on standing

(13.5g, 80%). This crude material could be used in the next step without further purification. A sample was purified by column chromotography on

Sorbsil ™ silica gel eluting with hexane:ethyl acetate :: 3:1 to give the desired product as a pale yellow solid, m.p. 54-56°C, which consisted of a mixture of keto-enol tautomers.

$\delta H(CDCl_3)$ 1.25(3H,t); 4.05(2H,d); 4.2(2H,q); 1.35(3H,t); 4.3(2H,q); 5.75(1H,s); 7.95 - 8.05(6x1H,m); 12.6(1H,s).

Step c: Preparation of 3-(2-fluoro-4-nitrophenyl)-5-hydroxy-1-methylpyrazole.

N-Methylhydrazine (10.91g) was added to a stirred solution of ethyl 3-(2-fluoro-4-nitrophenyl)-3-oxopropionate (55g), crude material, prepared as described in Step b, in ethanol (20 ml) over a period of 10 minutes keeping the temperature at less than 30°C. The reaction mixture was stirred at room temperature overnight. Diethyl ether was added to the reaction mixture and the resulting mixture stirred for approximately 30 minutes at room temperature. A resulting precipitate was filtered off, washed with diethyl ether and dried under suction to give the desired product (17.38g,34%). NMR indicated that no 5-phenyl isomer was present

δH(d_6 DMSO): 3.55(3H,s); 5.8(1H,d); 8.05(1H+1H+1H,m).

Step d: Preparation of 5-difluoromethoxy-3-(2-fluoro-4-nitrophenyl)-1-methylpyrazole.

Chlorodifluoromethane gas was bubbled through a mixture of 3-(2-fluoro-4-nitrophenyl)-5-hydroxy-1-methypyrazole, prepared as described in Step c, (15g) suspended in dichloromethane (200ml) until the mixture was saturated. 50% Aqueous sodium hydroxide solution (150ml) was added dropwise with vigorous stirring. The mixture was stirred for approximately 1 hour at room temperature and then 1 hour at 30°C. After cooling, the mixture was diluted with water. Two layers were separated and the aqueous phase extracted with dichloromethane. The combined organic phase and the dichloromethane extracts, were dried with anhydrous magnesium sulphate, filtered, and concentrated under *vacuo* to give a light brown residue, which was further purified by column chromatography on Sorbsil ™ silica gel eluting with hexane:ethyl acetate::3:1. Concentration under *vacuo* of the appropriate fractions gave the desired compound as a pale yellow solid (6.4g, 35%) m.p. 124-125°C.

δH ($CDCl_3$): 3.85(3H,s); 6.4(1H,t); 6.4(1H,s); 8.1(1H+1H,m); 8.3(1H,d).

Step e: Preparation of 4-chloro-5-difluoromethoxy-3-(2-fluoro-4-nitrophenyl)-1-methylpyrazole, (Compound 1 of Table I).

Sulphuryl chloride (3.62g) was added dropwise to a solution of 5-difluoromethoxy-3-(2-fluoro-4-nitrophenyl)-1-methylpyrazole, prepared as described in Step d, (7g) in acetonitrile (60 ml) while maintaining the internal temperature at less than 30°C. On completion of the addition, the reaction mixture was stirred at room temperature

for approximately a further 60 minutes and then poured into aqueous saturated sodium bicarbonate solution. The resulting mixture was extracted with diethyl ether (3x100ml). The combined ether extracts were washed with saturated aqueous sodium bicarbonate solution and water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a pale yellow solid (6.94g,77%) m.p 72-74°C.

δH($CDCl_3$): 3.85(3H,s); 6.7(1H,t); 7.75(1H,m); 8.1(1H+1H,m).

Compounds 3, 7, 9, 12, 24, 32 and 42 of Table I and 3-(4-chloro-2-fluorophenyl)-5-hydroxy-1-methylpyrazole were prepared by similar processes using appropriate starting materials.

EXAMPLE 2

This example illustrates the preparation of Compound 2 in Table I.

Titanium trichloride (30ml of 30% w/v solution in aqueous hydrochloric acid) was added dropwise to a stirred solution of Compound 1 in Table I, prepared as described in Example 1, (6.2g) in acetone (60 ml) while the internal temperature was maintained at less than 30°C. The progress of the reaction was monitored by the thin layer chromatography (TLC). On completion, when no more starting material remained in the reaction mixture, water was added and the mixture extracted with ethyl acetate (3x100ml). The combined ethyl acetate extracts were washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a brown residue, which was further purified by column chromatography on Sorbsil ™ silica gel, eluting with hexane: ethyl acetate:: 1:1. Concentration under *vacuo* of the appropriate fractions gave the desired compound as a light brown solid (4.6g, 82%), m.p.213°C decomposed.

δH(d_6-DMSO); 3.75(3H,s); 5.3(2H,br); 6.7(1H+1H,m); 7.3(1H,t); 7.25(1H,m).

EXAMPLE 3

This Example illustrates the preparation of Compound 4 in Table I.

Acetic anhydride (1ml) was added to a solution of Compound 2 in Table I, prepared as described in Example 2, (0.583g) in chloroform (5ml) and the mixture heated at reflux for 1 hour, when analysis by TLC indicated that no starting material remained. After cooling, the reaction mixture was diluted with chloroform, washed with water, dried over anhydrous magnesium sulphate and concentrated under *vacuo* to afford an off-white solid, which was

triturated with hexane, filtered and dried under *vacuo* to give a white solid, the desired compound, (0.434g, 66%) m.p. 174-176°C.

δH($CDCl_3$); 2.2(3H,s); 3.8(3H,s); 6.7(1H,t); 7.2(1H,m); 7.35(1H,br); 7.45(1H,m); 7.6(1H,m).

Compound 6 was prepared by a similar process using appropriate starting materials and reagents.

EXAMPLE 4

This Example illustrates the preparation of Compound 5 in Table I.

Potassium hydroxide pellets (0.168mg) were added to a solution of 4-chloro-5-difluoromethoxy-3-(4-cyano-2-fluorophenyl)-1-methylpyrazole, prepared as outlined in Example 1, (0.603g) in ethanol (0.168g) and the mixture was diluted with water and extracted with ethyl acetate. The combined ethyl acetate extracts were dried with anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give the desired product as an off-white solid, (0.420g,66%) mpt 139-141°C.

δH($CDCl_3$); 3.85(3H,s); 6.1(1H,br); 6.7(1H,t); 7.65(1H+1H+1H,m).

EXAMPLE 5

This Example illustrates the preparation of Compound 8 in Table I.

A few drops of concentrated sulphuric acid were added to a mixture of Compound 5 in Table I, prepared as described in Example 4, (0.600g) suspended in methanol (5ml) and the resulting mixture heated at reflux for approximately 5 hours. The reaction mixture was concentrated under *vacuo* and the residue partitioned between diethyl ether and water. The organic and aqueous phases were separated and the aqueous phase was further extracted with diethyl ether. The combined organic phase and ether extracts were dried over anhydrous magnesium sulphate, filtered, and concentrated under *vacuo*. The residue was purified by column chromotography on Sorbsil ™ silica eluting with hexane:ethyl acetate :: 3:1. Concentration of the relevant fractions under *vacuo* gave the desired product as a pale yellow viscous gum which solidified on standing

(0.246g, 39%), m.p.71-72°C.

δH($CDCl_3$); 3.85(3H,s); 3.95(3H,s); 6.7(1H,t); 7.6(1H,t); 7.85(1H+1H,m).

Compound 10 in Table I was prepared by a similar process using appropriate reagents and starting materials.

EXAMPLE 6

This Example illustrates the preparation of Compound 11 in Table I.

Oxalyl chloride (0.4ml) was added to a vigorously stirred suspension of Compound 5 from Table I, prepared as described in Example 4, (0.600g) in dichloromethane (2.0ml). A drop of dimethylformamide was added and the reaction mixture stirred for 3 hours at room temperature. The mixture was concentrated under *vacuo*. Concentrated aqueous ammonia solution was added to a stirred solution of the residue in dichloromethane and the reaction mixture was stirred for a further 2 hours at room temperature, during which time a precipitate formed. The precipitate was collected by filtration, washed with dichloromethane and dried to give the desired product

(0.320g, 54%), m.p. 207°C decomposed.

δH(d_6-DMSO) 3.85(3H,s); 6.8(1H,br); 6.9(1H,t); 7.85(1H,m); 7.9(1H+1H,m); 8.25(1H,br).

EXAMPLE 7

This Example illustrates the preparation of Compound 13 in Table I.

A mixture of Compound 2 in Table I, prepared as described in Example 2, (0.250g), dimethyldisulphide (1.88g) and t-butylnitrite (0.3ml) in dichloroethane (10ml) was warmed to initiate the reaction. Solutions of Compound 2 in Table I (2.25g) in dichloroethane and t-butylnitrite (2.7ml) were added dropwise simultaneously to the stirred reaction mixture at such a rate as to maintain the reaction temperature below 60°C. The reaction mixture was then stirred for a further 2 hours. Water was added. The organic phase was separated, washed with water, and then 2M aqueous hydrochloric acid, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a redish brown residue. The residue was further purified by column chromatography on Sorbsil ™ silica eluting with hexane:ethyl acetate :: 3:1. Concentration under *vacuo* of the appropriate fractions gave the desired product (1.04g, 36%).

δH($CDCl_3$); 2.5(3H,s); 3.8(3H,s); 6.7(1H,t); 7.15(1H,m); 7.3(1H+1H,m).

Compounds 37 and 38 were prepared in an analogous manner using appropriate starting materials and reagents.

EXAMPLE 8

This Example illustrates the preparation of Compound 14 in Table I.

Methanesulphonylchloride (0.240g) was added to a solution of Compound 2 in Table I, prepared as described in Example 2, (0.583g) and triethylamine (0.212g) in chloroform (5.0ml) and the mixture heated at reflux for 2 hours.

After cooling, the reaction mixture was diluted with chloroform, washed with water, dried over anhydrous magnesium sulphate, filtered, and concentrated under *vacuo* to give a brown residue. The residue was further purified by column chromatography on Sorbsil ™ silica eluting with hexane:ethyl acetate:: 1:1. Concentration of the appropriate fractions under *vacuo* gave the desired product as a pale yellow viscous oil, which solidified on standing (0.295g, 40%), m.p. 98-100°C.

δH($CDCl_3$); 3.1(3H,s); 3.85(3H,s); 6.7(1H,t); 7.05(1H+1H,m); 7.5(1H,m); 1.7(1H,b).

EXAMPLE 9

This Example illustrates the preparation of Compound 15 in Table I.

Step a: Preparation of 3-fluoro-4-(4-chloro-5-difluoromethoxy-1-methylpyrazol-3-yl)-phenyldiazonium tetrafluoroborate salt.

A solution of sodium nitrite (1.55g) in water (10 ml) was added dropwise to a stirred suspension of Compound 2 in Table I, prepared as described in Example 2, (5.0g) in water (50ml) at 0°C, and the resulting mixture was stirred for approximately a further 20 minutes at 0°C. 50% aqueous hydrotetrafluoroboric acid (20ml) was added to the vigorously stirred reaction mixture at 0°C.

After warming to room temperature the desired product had precipitated and was recovered by filtration and dried by suction (6.5g). The product was used without further purification.

Step b:

The diazonium salt, prepared as described in Step a, (6.5g) was added to a vigorously stirred solution of copper (II) nitrate trihydrate (92.35g) in water (170ml) and the resulting mixture was stirred at room temperature for 1 hour. Copper (I) oxide (0.924g) was added to the reaction mixture, which became frothy. After stirring for a further hour at room temperature, the reaction mixture was extracted with dichloromethane (2x150ml). The

organic extracts were washed with water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a brown gum (4.4g, 88%) which could be used in other reactions without further purification. A sample of the residue (1g) was further purified by column chromatography on Sorbsil ™ silica eluting with hexane:ethyl acetate :: 1:1. Concentration under *vacuo* of the appropriate fractions gave the desired compound as a redish brown viscous gum (0.194g).

δH($CDCl_3$); 3.8(3H,s); 6.25(1H,br); 6.6(1H+1H,m); 6.7(1H,t); 7.35(1H,m).

EXAMPLE 10

This Example illustrates the preparation of Compound 16 in Table I.

Ethyl bromoacetate (0.586g) and anhydrous potassium carbonate (0.483g) were added to a solution of Compound 15 in Table I, prepared as described in Example 9, (1.02g) in acetone (10ml) and the mixture heated at reflux for 2 hours. After cooling, the reaction mixture was filtered and concentrated under *vacuo*.

The residue was dissolved in ethyl acetate, washed with water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a brown residue. The residue was further purified by column chromatography on Sorbsil ™ silica eluting with hexane:ethyl acetate:: 2:1. Concentration of the appropriate fractions gave the desired products as a redish viscous gum (0.456g, 35%).

δH($CDCl_3$): 1.3(3H,t); 3.8(3H,s); 4.25(2H,q); 4.65(2H,s); 6.7(1H,t); 6.75(1H+1H,m); 7.45(1H,t).

Compounds 21, 27, 28, 29 and 30 in Table I was prepared by a similar process using appropriate starting materials and reagents.

EXAMPLE 11

This Example illustrates the preparation of Compound 17 in Table I.

Methanesulphonylchloride (0.216g) was added to a solution of Compound 15 in Table I, prepared as described in Example 9, (0.500g) and triethylamine (0.190 g) in chloroform (5ml) and the mixture heated at reflux for 2 hours. After cooling, the mixture was diluted with chloroform, washed with water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a light brown residue. The residue was purified by column chromatography on Sorbsil ™ silica eluting with hexane:ethylacelate :: 1:1. Concentration of

the appropriate fractions under *vacuo* gave the desired product as a pale yellow viscous gum (0.343g, 54%).

δH($CDCl_3$); 3.2(3H,s); 3.85(3H,s); 6.7(1H,t); 7.2(1H+1H,m); 7.6(1H,t).

EXAMPLE 12

This Example illustrates the preparation of Compound 18 in Table I.

Step a: Preparation of 3-(4-chloro-2-fluorophenyl)-1-methyl-5-thiopyrazole.

A mixture of 3-(4-chloro-2-fluorophenyl)-5-hydroxy-1-methylpyrazole, prepared by a similar process using appropriate reagents as described in Example 1 Step c, (4.76g) and Lawesson's reagent, 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulphide (5.08g) in xylene (80ml) was heated at reflux for 5 hours. After cooling water was added and the resulting organic and aqueous phases separated. The aqueous phase was extracted with ethyl acetate. The combined organic phase and ethyl acetate extracts, were washed with water, dried over anhydrous magnesium sulphate, filtered, and concentrated under *vacuo* to give an orange-red residue which, on trituration with hexane, gave a pale yellow solid (5.9g) which was used without further purification.

Step b: Preparation of 5-difluoromethylsulphide-3-(4-chloro-2-fluorophenyl)-1-methylpyrazole.

This compound was prepared from the product of Step a of this Example (5.7g) in a similar process to that described in Example 1, Step d using appropriate reagents and starting materials, as a pale yellow solid, (2.14g, 35%), m.p. 60-62°C.

δH($CDCl_3$); 4.0(3H,s); 6.75(1H,t); 7.0(1H,d); 7.15(1H+1H,m); 7.9(1H,m).

Step c: Preparation of 4-chloro-5-difluoromethylsulphide-3-(4-chloro2-fluorophenyl)-1-methyl-pyrazole, Compound 18 in Table I.

The compound was prepared from the product of Step b above (1.56g) by a similar process to that described in Step e of Example 1, using appropriate reagents and starting materials. The product was obtained as a pale yellow viscous gum (1.49g).

δH($CDCl_3$); 4.05(3H,s); 6.8(1H,t); 7.2(1H+1H,m); 7.5(1H,m).

EXAMPLE 13

This Example illustrates the preparation of Compound 19 in Table I.

m-Chloroperbenzoic acid (0.763g)was added to a solution of Compound 18 in Table I, prepared as described in Example 12 (0.978g) in chloroform (30ml) and the mixture heated at

reflux overnight. After cooling the reaction mixture was washed with aqueous sodium bisulphite solution and aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulphate and concentrated under *vacuo*. The residue was purified by column chromotography on Sorbsil ™ silica eluting with hexane:ethyl acetate:: 3:1. Concentration of the appropriate fractions under *vacuo* gave the desired compound as a solid (0.490g,41%), m.p. 82-84°C.

δH ($CDCl_3$): 4.2(3H,s); 6.7(1H,t); 7.25(1H+1H, m); 7.5(1H,m).

Compound 23 was prepared by a similar process using appropriate starting materials, reagents and conditions.

EXAMPLE 14

This Example illustrates the preparation of Compound 20 in Table I.

m-Chloroperbenzoic acid (0.356g) was added to a stirred solution of Compound 13 in Table I, prepared as described in Example 7, (0.555g) in dichloromethane (45ml) and the mixture heated at reflux for 3 hours. After cooling, the mixture was washed with aqueous sodium bisulphite solution and then with aqueous sodium bicarbonate solution, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a gum which was purified by column chromatography on Sorbsil ™ silica gel eluting with hexane:ethyl acetate::1:2. Concentration of the appropriate fractions under *vacuo*, gave the desired product as a pale yellow gum (0.238g,, 41%).

δH ($CDCl_3$): 2.8(3H,s); 3.9(3H,s); 6.7(1H,t); 7.5(1H+1H,m); 7.7(1H,m).

Compounds 35 and 36 were prepared in an analogous manner using appropriate starting materials and reagents.

EXAMPLE 15

This Example illustrates the preparation of Compound 22 in Table I.

This compound was prepared from Compound 15 in Table I, prepared as described in Example 9, (0.8g) by an analogous process to that described in Step d of Example 1, using appropriate starting materials and reagents, to give a pale yellow viscous gum (0.474mg, 51%).

^{1}H NMR ($CDCl_3$): 3.8(3H,s); 6.55(1H,t); 6.7(1H,t); 7.0(1H+1H,m); 7.5(1H,m).

EXAMPLE 16

This example illustrates the preparation of Compound 25 in Table I.

Bromine (0.68g) was added dropwise at room temperature to a stirred solution of 5-difluoromethoxy-3-(2-fluoro-4-trifluoromethylphenyl)-1-methylpyrazole, (0.923g), prepared as described in Example 1, Step d, using appropriate starting materials and reagents, anhydrous sodium acetate (0.700g) and water (1.0ml) in glacial acetic acid (15ml). On completion of the addition, the reaction mixture was stirred overnight at room temperature, then poured into ice/water and the resulting aqueous phase extracted with ethyl acetate (3x20ml). The combined organic extracts were washed with aqueous sodium thiosulphate solution and water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give the desired product as a pale orange gum (0.598g, 49%).

δH($CDCl_3$): 3.9(3H,s); 6.7(1H,t); 7.45(1H+1H,m); 7.65(1H,m).

Compounds 39 and 41 were prepared in analogous manner using appropriate starting materials and reagents.

EXAMPLE 17

This example illustrates the preparation of Compound 26 in Table I.

Step a: Preparation of Methyl 2-fluoro-4-(2-trimethysilylethynyl)-benzoate.

Bis(triphenylphosphine) palladium dichloride (1.12g) and copper (I) iodide (0.080g) were added to a solution of methyl 4-bromo-2-fluorobenzoate (17.68g) and trimethylsilylacetylene (9.44g) in triethylamine (300ml). The resulting mixture was stirred at room temperature under a atmosphere of dry nitrogen for approximately 5 hours. The reaction mixture was filtered and concentrated under *vacuo*. The residue was purified by column chromatography on Sorbsil™ silica gel eluting with hexane:ethyl acetate:: 4:1. Concentration under *vacuo* of the appropriate fractions gave the desired product as brown liquid (12.0g) which was used without further purification.

Step b Preparation of potassium 4-ethynyl-2-fluorobenzoate.

5% Aqueous potassium hydroxide solution (60ml) was added to a solution of crude methyl 2-fluoro-4-(2-trimethylsilylylethynyl)-benzoate, prepared as described in Step a of this example, (12g) in methanol (60ml) and the mixture stirred at room temperature for 1 hour. The mixture was concentrated under *vacuo* and the residue triturated with acetone. After

drying, the crude desired product was obtained as a buff solid (11.0g) which was used without further purification.

Step c: Preparation of 4-ethynyl-2-fluorobenzoyl chloride.

A mixture of the crude potassium 4-ethynyl-2-fluorobenzoate, prepared as described in Step a of this example, (11g) in thionyl chloride (150ml) was heated at reflux for 3 hours. Excess thionyl chloride was removed under *vacuo* and the crude product obtained as a brown residue (11.0g) was used directly without further purification.

Step d: Preparation of ethyl 3-(4-ethynyl-2-fluorophenyl)-3-oxopropionate.

Triethylamine (14.91g) and magnesium dichloride (15.93g) were added successively to a vigorously stirred solution of potassium ethyl malonate (23.95g) in acetonitrile (110ml) at 10°C under an inert atmosphere of nitrogen. After stirring for a further 2½ hours at room temperature the mixture was cooled to 0°C, and the crude 4-ethynyl-2-fluorobenzoyl chloride, prepared as described in Step c of this example, (11.0g) was added dropwise over approximately 15 minutes. After the addition of the benzoyl chloride was complete, triethylamine (1.49g) was added and the mixture allowed to warm to room temperature. After stirring overnight at room temperature, the mixture was concentrated under *vacuo*, the residue mixed with ethyl acetate and the resulting mixture cooled to 10°C. 2M Hydrochloric acid (100ml) was added to the mixture with vigorous stirring with the temperature kept at less than 25°C. The resulting aqueous and organic phases were separated, and the aqueous was extracted with ethyl acetate. The combined organic phases were washed with 2M hydrochloric acid and water, dried over anhydrous magnesium sulphate, and concentrated under *vacuo* to give the crude product as orange liquid residue (23g) which was used directly without further purification.

Step e: Preparation of 3-(4-ethynyl-2-fluorophenyl)-5-hydroxyl-1-methylpyrazole.

Methylhydrazine (4.52g) was added dropwise over a period of approximately 15 minutes to a solution of crude ethyl 3-(4-ethynyl-2-fluorophenyl)-3-oxopropionate, prepared as described in Step d of this example, (23.0g) in ethanol (10ml) with the internal temperature kept at less than 30°C. After stirring at room temperature overnight, diethyl ether was added and the mixture stirred for a further 30 minutes at room temperature, during which time a precipitate formed which was collected by filtration, washed with

ethanol/diethyl ether and dried. The precipitate (5.42g) was predominantly the desired product and was used directly without further purification.

Step f: Preparation of 5-difluoromethoxy-3-(4-ethynyl-2-fluorophenyl)-1-methylpyrazole.

50% Aqueous sodium hydroxide solution (50ml) was added dropwise with vigorous stirring to a suspension of crude 3-(4-ethynyl-2-fluorophenyl)-5-hydroxy-1-methylpyrazole, prepared as described in Step e of this example, (5.0g) in dichloromethane (50ml) containing tetraphenyl phosphonium bromide (5.04g) and saturated with chlorodifluoromethane gas. After stirring for 1 hour at room temperature, the reaction mixture was diluted with water the aqueous and organic phases separated and the aqueous phase extracted with dichloromethane. The combined organic phases were washed with water, dried over anhydrous magnesium sulphate, dried and concentrated under *vacuo* to give a dark brown residue. The residue was further purified by column chromatography on Sorbsil™ eluting with hexane:ethyl acetate :: 3:1. Concentration of the appropriate fractions under *vacuo* gave the desired compound as a gum (1.75g, 9% overall).

δH($CDCl_3$): 3.15(1H,s); 3.85(3H,s); 6.7(1H,t); 7.3(1H+1H,m); 7.5(1H,t).

Step g: Preparation of Compound 26 in Table I.

Sulphuryl chloride (0.977g) was added dropwise to a stirred solution containing 5-difluoromethoxy-3-(4-ethynyl-2-fluorophenyl)-1-methylpyrazole, prepared as described in Step f (1.75g) and triethylamine (0.731g) in acetonitrile (20ml) maintained at less than 10°C. After warming to room temperature, the reaction mixture was stirred at room temperature for a further 1 hour, then poured into saturated aqueous sodium bicarbonate solution and extracted with diethyl ether (3x30ml). The diethyl ether extracts were combined, washed with saturated aqueous sodium bicarbonate solution and water, dried over anhydrous magnesium sulphate, filtered, and concentrated under *vacuo* to give a pale orange residue, which was further purified by column chromatography on Sorbsil™ silica eluting with hexane:diethyl ether :: 3:1. Concentration under *vacuo* of the appropriate fractions gave the desired product as a colourless gum which solidified on standing to afford a white crystalline solid (0.270g, 14%) m.p. 50-51°C.

δH($CDCl_3$): 3.15(1H,s); 3.85(3H,s); 6.7(1H,t); 7.3(1H+1H,m); 7.5(1H,t).

EXAMPLE 18

This example describes the preparation of Compound 31 in Table I.

Step a: Preparation of ethyl 2-(3-(4-chloro-2-fluorophenyl)-1-methylpyrazol-5-yloxy)-acetate.

Ethyl bromoacetate (0.200g) was added to a stirred mixture containing 3-(4-chloro-2-fluorophenyl)-5-hydroxy-1-methylpyrazole (0.266g), prepared in a similar manner to that described in Step c of Example 1 using appropriate reagents, and potassium carbonate (0.276g) in 2-butanone (5ml). The reaction mixture was heated at 90°C for 1 hour until analysis by thin layer chromatography indicated that no starting pyrazole remained. After cooling, the reaction mixture was diluted with diethyl ether and filtered. The filtered solid was washed with diethyl ether and the combined filtrates concentrated under *vacuo*. The residue was further purified by column chromatography on silica eluting with ethyl acetate:hexane :: 1:1. Concentration of the appropriate fractions gave the desired product as a slowly crystallising solid (0.248g, 79%).

δH($CDCl_3$): 1.32(3H,t); 3.79(3H,s); 4.30(2H,q); 4.69(2H,s); 5.94(1H,s); 7.12 (1H +1H, m); 7.90 (1H, m).

Step b: Preparation of Compound 31 in Table I.

N-Bromosuccinimide (0.217g) was added to a solution of ethyl 2-(3-(4-chloro-2-fluorophenyl)-1-methylpyrazol-5-yloxy)-acetate, prepared as described in Step a of this example, (0.380g) at room temperature. The reaction mixture was heated at reflux by illumination with a tungsten lamp and the reaction progress monitored by GLC. A further portion of N-bromosuccinimide (approximately 0.044g) was required to force the reaction to completion. After cooling, the reaction mixture was concentrated under *vacuo* and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with water and saturated sodium chloride solution, dried over anhydrous magnesiun sulphate, filtered and concentrated under *vacuo* to give the desired compound as an orange brown crystalline solid (0.430g, 90%) m.p. 85-86°C.

δH($CDCl_3$) 1.31(3H, t); 3.89(3H, s); 4.28(2H, q); 4.97(2H, s); 7.19(1H+1H, m); 7.47(1H,m).

Compound 33 (m.p. 58-59°C) was also prepared in an analogous manner using appropriate starting materials.

EXAMPLE 19

This example describes the preparation of Compound 34 in Table I.

Step a: Preparation of 5-chloro-3-(4-chloro-2-fluorophenyl)-1-methylpyrazole.

A mixture of phosphorous oxytrichloride (0.368g) and 3-(4-chloro-2-fluorophenyl)-5-hydroxy-1-methylpyrazole, prepared as described in Example 1, (0.224g) was stirred and heated at 110°C for 5 hours. After stirring for a further 15 minutes at room temperature, the reaction mixture was extracted with ethyl acetate (2x10ml). The combined organic extracts were washed with water and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure to give a green oil (0.150g) as a residue. The residue was further purified by column chromatography on silica eluting with ethyl acetate. Concentration of the appropriate fractions under *vacuo* gave the desired product as a brown crystalline solid (50mg, 21%) m.p. 62-63°C.

Step b: Preparation of Compound 34 in Table I.

Sulphuryl chloride (0.097g) was added in one portion to a stirred solution of 5-chloro-3-(4-chloro-2-fluorophenyl)-1-methylpyrazole, prepared as described in Step a of this example, (0.176g) in dry acetonitrile (8ml) under a dry inert nitrogen atmosphere at room temperature. After one hour, no starting material remained by either TLC or GLC. The reaction mixture was diluted with diethyl ether (20ml), washed carefully twice with saturated aqueous sodium bicarbonate solution and once with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered, and concentrated under *vacuo* to give the desired product as a cream coloured cryalline solid (0.196g, 98%) m.p. 96-97°C. δH($CDCl_3$) 3.91(3H, s); 7.12 (1H+1H, m); 7.90(1H, m).

EXAMPLE 20

This example describes the preparation of Compound 40 in Table I.

Step a: Preparation of 4-chloro-3-(4-dibromomethyl-2-fluorophenyl)-5-difluoromethoxy-1-methylpyrazole.

N-Bromosuccinimide (1.35g) and a catalytic amount of benzoyl peroxide were added to a solution of 4-chloro-5-difluoromethoxy-1-methyl-3-(4-methyl-2-fluorophenyl)pyrazole, compound 32 in Table I, prepared as described in Example 1, (1.0g) in carbon tetrachloride (15ml) and the resulting mixture heated at reflux for 5 hours. After cooling, the mixture was

filtered and the filtrate concentrated under *vacuo* to give the crude product which was used directly without further purification.

Step b: Preparation of 4-chloro-5-difluoromethoxy-3-(4-formyl-2-fluorophenyl)-1-methylpyrazole.

A suspension of the crude 4-chloro-3-(4-dibromomethyl)-2-fluorphenyl)-5-difluoromethoxyl-1-methylpyrazole, prepared as described in Step a of this example, (0.897g) in concentrated hydrochloric acid (3ml) was heated at reflux for 5 hours and the reaction monitored by TLC. After cooling the reaction mixture was poured into ice/water and the resulting mixture extracted with ethyl acetate (3x10ml). The combined ethyl acetate extracts were washed with 5% aqueous sodium bicarbonate solution and water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo*. The residue was further purified by column chromatography on Sorbsil™ silica eluting with hexane:diethyl ether::3:1.

Concentration of the appropriate fractions gave the desired product as a gum.

δH($CDCl_3$): 3.85(3H,s); 6.7(1H,t); 7.7(1H+1H+1H, m); 10.0(1H,s).

Step c: Preparation of Compound 40.

An aqueous 2M sodium hydroxide solution (18ml) was added to a solution containing 4-chloro-5-difluoromethoxy-3-(4-formyl-2-fluorophenyl)-1-methylpyrazole (1.0g), prepared as described in Step b of this Example, and methyl triphenylphosphonium iodide (2.65g) in toluene (8ml) and the mixture stirred at room temperature for 24 hours. Ethyl acetate was added to the reaction mixture and the organic and aqueous phases separated. The aqueous phase was further extracted with ethyl acetate. The combined organic phases were washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a pale orange solid residue. The residue was further purified by column chromatography on Sorbsil™ silica eluting with hexane:diethyl ether::4:1. Concentration of the appropriuate fractions under *vacuo* gave the desired product as a pale yellow viscous gum.

δH($CDCl_3$): 3.85(3H,s); 5.35(1H,d);. 5.8(1H,d); 6.7(1H,t); 6.75(1H,m); 7.2(1H+1H,m); 7.5(1H,m).

EXAMPLE 21

This example describes the preparation of Compound 43 in Table I.

Step a: Preparation of 4-chloro-3-(4-chloro-5-chlorosulphonyl-2-fluorophenyl)-5-difluoromethoxy-1-methoxypyrazole.

A mixture of 4-chloro-3-(4-chloro-2-fluorophenyl)-5-difluoromethoxy-1-methylpyrazole, prepared as described in Example 1, (1.3g) and chlorosulphonic acid were heated at 110°C to 120°C for 3 hours. After cooling, the reaction mixture was carefully poured into ice. The resulting aqueous mixture was extracted with ethyl acetate (3x20ml). The combined extracts were washed with water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a mixture of 2 compounds as a brown solid (0.945g) which was used directly without further purification.

Step b: Preparation of Compound 43.

Crude 4-chloro-3-(4-chloro-5-chlorosulphonyl-2-fluorophenyl)-5-difluoromethoxy-1-methylpyrazole, prepared as described in Step a of this example (0.930g) was added to a mixture containing dioxane (15ml), water (1.5ml) and potassium fluoride (0.264g) and the resulting mixture heated at reflux for 3 hours. After cooling, the reaction mixture was poured onto ice/water and extracted with diethyl ether (3x20ml). The combined organic extracts were washed with water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a yellow gum which solidified on standing. The residue was triturated with hexane, filtered and dried to give the desired product as a solid (0.280g, 31%) m.p. 58-60°C.

$\delta H(CDCl_3)$: 3.85(3H,s); 6.7(1H,t); 7.5(1H,d); 8.4(1H,d).

$\nu (SO_2F)$: 1416cm^{-1}, 1215cm^{-1}.

EXAMPLE 22

This example describes the preparation of Compound No. 44 in Table 1.

Step a: Preparation of 4-bromo-5-difluoromethoxy-3-(4-fluoro-2-methoxyphenyl)-1-methylpyrazole.

Anhydrous sodium acetate (1.94g) and water (2.0ml) were added to a solution of 5-difluoromethoxy-3-(4-fluoro-2-methoxyphenyl)-1-methylpyrazole, prepared in an analogous manner to that of Example 1 Steps a to d, (2.68g) in glacial acetic acid (40ml) and the mixture stirred at room temperature for 20 minutes before adding bromine (1.88g) dropwise

over 15 minutes. After stirring at room temperature overnight, the reaction mixture was poured into ice/water (100ml) and extracted with diethyl ether (2x100ml). The organic extracts were combined, washed with water and then saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give an orange oil (3.61g), which was used directly without further purification.

Step b: Preparation of 4-chlorosulphonyl-5-difluoromethoxy-3-(4-fluoro-2-methoxyphenyl) 1-methylpyrazole.

A 1.6M solution of n-butyl lithium in hexane (5.2ml) was added over 5 minutes to a stirred solution of crude 4-bromo-5-difluoromethoxy-3-(4-fluoro-2-methoxyphenyl)-1-methylpyrazole, prepared as described in Step a, (2.61g) in dry diethyl ether (100ml) cooled to -70°C under a dry inert atmosphere of nitrogen. The stirred reaction mixture was allowed to warm to -55°C for ½ hour then transferred to a flask containing condensed sulphur dioxide in dry diethyl ether (50ml) cooled to -70°C. On mixing, the temperature rose to -50°C and the reaction mixture was cooled to -70°C then allowed to warm to room temperature over 1 hour, and a precipitate formed.

After standing at room temperature for 72 hours, the reaction mixture was concentrated under *vacuo* to give a residue which was triturated with dry diethyl ether (20ml). The resulting solid was collected by filtration, washed with diethyl ether (2x25ml) and air dried to give an off white powdery solid (1.1g).

The solid (1.1g) was taken up into diethyl ether (25ml) at room temperature under nitrogen and thionyl chloride (0.48g) added dropwise. After stirring for 2 hours at room temperature, the reaction mixture was washed with water, twice with saturated aqueous sodium bicarbonate solution, then with water, 2M aqueous hydrochloric acid solution, twice with water, and with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to a waxy solid (0.6g), which was used directly without further purification.

Step c: Preparation of compound 44.

A solution of anhydrous potassium fluoride (0.18g) in water (1ml) was added to a solution of crude 4-chlorosulphonyl-5-difluoromethoxy-3-(4-fluoro-2-methoxyphenyl)-1-methylpyrazole, prepared as described in Step b, (0.57g) in dioxane (10ml) and the resulting mixture stirred and heated to 100-110°C for 3 hours. After cooling, the reaction mixture was

poured into water and extracted with diethyl ether (20ml) and ethyl acetate (10ml). The combined organic extracts were washed with water and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a dark oil (0.38g). The oil was further purified by column chromatography on silica eluting with diethyl ether:hexane::3:7. Concentration of the appropriate fractions under *vacuo* gave the desired compound as a waxy solid containing 10% each of the 4-bromo and 4-chloro substituted pyrazole analogues by GLC (0.2g).

δH ($CDCl_3$): 3.81(3H,s); 3.90(3H,s); 6.85(1H,t); 6.72 (1H+1H, m); 7.33(1H, m).

EXAMPLE 23

This example describes the preparation of Compound No 45 in Table 1.

Step a: Preparation of 4-chloro-5-difluoromethoxy-3-(4-chlorosulphonyl-2-fluorophenyl) -1-methylpyrazole.

Compound 2 in Table 1, prepared as described in Example 2, (3.85g) was added with stirring to a mixture of acetic acid (3ml) and concentrated hydrochloric acid (10ml) and a precipitate of a hydrochloride salt formed. The mixture was cooled to less than -5°C and a solution of sodium nitrite (1.0g) in water (1ml) added maintaining the temperature of the reaction mixture at less than 0°C.

Sulphur dioxide was bubbled through acetic acid (30ml)until the solution was saturated. After the addition of copper (I) chloride (0.327g) further sulphur dioxide was bubbled through the solution until the yellow green suspension turned blue green. After cooling to approximately 10°C the diazotisation reaction mixture was added to the copper suspension portionwise. When the addition of the diazotisation reaction mixture was complete, the reaction mixture was allowed to warm to room temperature and stirred for a further 30 minutes at room temperature, before being poured onto ice and extracted with diethyl ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate solution until neutral, then with water and dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a dark brown residue, which was fractioned by column chromatography on Sorbsil ™ silica eluting with hexane:ethyl acetate::2:1. Concentration under *vacuo* gave the desired compound as a gum (2.0g, 40%).

δH ($CDCl_3$): 3.85(3H,s); 6.7(1H,t); 7.85(1H+1H+1H,m).

Step b: Preparation of Compound No. 45

A solution of potassium fluoride (0.620g) in water (3ml) was added to a solution of 4-chloro-5-difluoromethyloxy-3-(4-chlorosuphonyl-2-fluorophenyl)-1-methylpyrazole (2.0g), prepared as described in Step a, in dioxane (30ml) and the mixture heated at reflux for 3 hours. After cooling to room temperature, the reaction mixture was poured into ice/water and extracted with diethyl ether (3x50ml). The combined organic extracts were washed with water, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give an orange yellow gum, which was further purified by column chromatography on Sorbsil ™ silica gel eluting with hexane:ethyl acetate::3:1. Concentration of the appropriate fractions under *vacuo* gave the desired product as a solid (0.41g, 21%) m.p. 52-53°C.

δH ($CDCl_3$): 3.9(3H,s); 6.7(1H,t); 7.85(1H+1H+1H,m).

EXAMPLE 24

This example describes the preparation of Compound No. 46 in Table 1.

Step a: Preparation of 4-carboxy-3-(4-chloro-2-fluorophenyl-5-difluoromethoxy-1-methylpyrazole.

A 1.6M solution of n-butyl lithium in hexane (2.06) was added over one minute to a stirred solution of crude 4-bromo-5-difluoromethoxy-3-(4-fluoro-2-methoxyphenyl)-1-methylpyrazole, prepared as described in Example 22, Step a, (1.06g) in dry diethyl ether (40ml) under an inert atmosphere of nitrogen cooled to -73°C.

The stirred reaction mixture was allowed to warm to -60°C for 10 minutes, cooled to -70°C and then poured onto crushed solid carbon dioxide. After the carbon dioxide had evaporated, the residue was diluted with diethyl ether (50ml). The organic phase was washed twice with 2M aqueous hydrochloric acid solution and then extracted with saturated aqueous sodium bicarbonate solution (2x15ml). The aqueous extracts were combined, washed with diethyl ether, carefully acidified with 2M aqueous hydrochloric acid solution, and extracted with diethyl ether (2x30ml). The combined ether extracts were washed with water and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a pale yellow solid (0.3g) which was further purified by column chromatography on silica eluting with ethyl acetate:hexane::1:1. Concentration of the appropriate fractions under *vacuo* gave the desired product as a pale yellow crystalline solid (0.2g, 30%) m.p. 149-50°C.

Step b: Preparation of Compound No. 46.

One drop of dimethylformamide and then, in one portion, oxalyl chloride (0.114g) were added to a stirred solution of 4-carboxy-3-(4-chloro-2-fluorophenyl)-5-difluoromethoxy-1-methylpyrazole, prepared as described in Step a, (0.260g) in dry dichloromethane under an inert nitrogen atmosphere. After stirring for 2 hours at room temperature triethylamine (0.101g) and ethanol (2.0ml) were added. After 2½ hours at room temperature, the reaction mixture was concentrated under *vacuo* and the residue mixed with water (20ml).

The aqueous mixture was extracted with ethyl acetate (2x30ml). The combined organic extracts were washed with water and saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and concentrated under *vacuo* to give a yellow oil (0.210g) which was further purified by column chromatography on silica eluting with hexane:diethyl ether ::2:1. Concentration of the appropriate fractions gave a slowly crystallising solid, m.p. 54-5°C (0.11g) which was predominantly the desired product (93%) but also contained a detectable impurity (probably diethyl oxalate).

δH ($CDCl_3$): 1.17(3H,t); 3.85(3H,s); 4.20(2H,q); 6.83(1H,t); 7.18 (1H +1H, m); 7.41 (1H, m).

Biological Data

The herbicidal activity of the compounds was tested as follows: each chemical was formulated in one of two ways. Either the chemical was dissolved in an appropriate amount of water, dependent on the amount of solvent/surfactant blend required such that the total volume is $5cm^3$. Then a solvent sufficient blend comprised 78.2 gm/litre of Tween 20 and 21.8 gm/litre of Span 80 adjusted to 1 litre using methylcyclohexanone was added to the solution. Alternatively, the chemical was dissolved in water to the required concentration and 0.1% Tween added. Tween 20 is a Trade Mark for a surface-active agent comprising a condensate of 20 molar proportions of ethylene oxide with sorbitan laurate. Span 80 is a Trade Mark for a surface-active agent comprising sorbitan mono-laurate. If the chemical did not dissolve, the volume was made up to $5cm^3$ with water, glass beads were added and this mixture was then shaken to effect dissolution or suspension of the chemical, after which the beads were removed. In all cases, the mixture was then diluted to the required spray volume. If sprayed independently, volumes of $25cm^3$ and $30cm^3$ were required for post-emergence

tests; if sprayed together, 45cm^3 was required. The sprayed aqueous emulsion contained 4% of the initial solvent/surfactant mix and the test chemical at an appropriate concentration.

The spray compositions so prepared were sprayed on to young pot plants (post-emergence test) at a spray volume equivalent to 1000 litres per hectare. Damage to plants was assessed 13 days after spraying by comparison with untreated plants, on a scale of 0 to 9 where 0 is 0% damage, 1 is 1-5% damage, 2 is 6-15% damage, 3 is 16-25% damage, 4 is 26-35% damage, 5 is 36-59% damage, 6 is 60-69% damage, 7 is 70-79% damage, 8 is 80-89% damage and 9 is 90-100% damage.

In a test carried out to detect pre-emergence herbicidal activity, crop seeds were sown at 2 cm depth and weed seeds at 1 cm depth beneath compost and sprayed with the compositions at the rate of 1000 litres per hectare. 20 days after spraying, the seedlings in the sprayed plastic trays were compared with the seedlings in unsprayed control trays, the damage being assessed on the same scale of 0 to 9.

The results of the tests are given in Table II below for compounds 1 to 23.

Similar tests were carried out for compounds 24 to 46. For these compounds, only pre-emergence tests were carried out, the application rate was, in each case 125g per hectare and all the results were measured 20 dayss after spraying. The results of these experiments are shown in Table III.

TABLE II

Compd	Pre/ Post	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
1	Post	8	4	4	6	5	3	9	5	9	6	9	9	9	8	2	3	4	4	5	2	5	9	5	5
	Pre	6	5	2	4	0	0	9	-	9	-	9	9	5	8	2	5	8	6	5	9	9	9	9	0
2	Post	3	0	3	2	1	0	3	0	5	3	4	5	2	2	0	0	0	2	2	1	2	2	1	0
	Pre	2	2	0	0	0	0	0	0	0	-	0	0	2	0	6	0	0	0	0	0	0	0	0	0
3	Post	6	4	5	3	2	3	8	6	9	6	9	9	9	6	2	3	2	3	4	5	5	6	2	3
	Pre	5	0	0	4	0	1	6	6	9	9	9	9	3	5	2	3	3	5	5	2	6	8	5	0
4	Post	1	2	1	1	0	0	1	0	6	1	7	5	1	1	0	0	0	0	1	0	0	0	0	0
	Pre	3	0	0	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0	3	0
5	Post	3	4	2	2	1	2	1	0	6	5	6	9	6	3	2	0	2	1	2	2	1	4	3	2
	Pre	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	Post	0	0	0	1	0	0	2	0	2	2	5	0	3	3	0	2	1	0	1	0	0	0	0	0
	Pre	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	Post	5	4	4	2	0	1	3	0	9	7	9	9	6	6	3	2	2	1	4	9	5	5	3	2
	Pre	2	0	2	0	0	0	3	2	9	7	9	9	3	4	0	1	0	0	4	9	5	5	7	0
8	Post	8	4	5	2	2	2	6	2	9	5	9	9	9	6	4	0	1	2	4	3	3	3	2	3
	Pre	0	0	0	0	0	0	5	0	7	-	5	6	3	0	0	2	2	0	0	3	0	2	0	3
9	Post	7	4	6	2	2	2	6	0	9	5	9	9	9	6	5	0	2	0	5	7	4	5	3	3
	Pre	6	2	0	0	0	0	5	2	9	0	9	9	2	3	0	0	0	0	2	9	5	6	6	0
10	Post	0	0	0	2	0	0	1	0	1	1	0	9	0	2	0	0	0	0	0	0	0	0	0	0
	Pre	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE II Contd.

Compd	Pre/ Post	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
11	Post	4	3	2	2	0	0	2	0	9	5	8	9	1	3	1	0	1	0	1	1	1	4	3	0
	Pre	0	0	0	0	0	0	-	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12	Post	9	9	9	7	5	9	9	9	9	9	9	9	9	9	9	9	5	9	9	9	9	9	9	5
	Pre	9	9	5	6	3	6	9	9	9	6	9	9	9	9	-	9	9	9	9	9	9	9	9	2
14	Post	2	2	3	2	0	0	2	0	9	0	6	5	2	0	0	0	0	0	2	2	0	2	3	0
	Pre	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
15	Post	0	0	2	2	0	0	2	0	6	2	6	0	0	0	0	1	1	1	2	2	0	0	1	0
	Pre	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
16	Post	4	5	5	2	1	1	5	6	8	8	9	9	9	9	5	3	3	1	2	2	3	5	2	0
	Pre	0	0	0	2	0	2	0	0	5	5	0	9	0	0	0	0	0	0	0	0	0	0	0	0
17	Post	5	2	2	2	1	2	4	0	6	8	9	9	6	4	2	2	0	0	3	2	2	3	2	1
	Pre	0	0	2	2	0	1	5	3	9	6	6	6	2	3	-	0	2	0	0	6	2	0	2	0
18	Post	9	3	4	3	2	3	9	9	9	8	9	9	7	9	5	3	2	3	3	4	5	9	5	3
	Pre	9	3	0	2	0	1	9	6	9	6	9	9	5	9	0	4	7	7	7	9	9	9	9	0
19	Post	9	4	9	2	2	3	9	9	9	9	9	9	9	9	5	3	2	5	6	9	4	9	7	
	Pre	9	9	2	0	0	0	9	9	9	9	9	9	9	7	3	3	5	8	9	9	9	9	9	0
20	Post	9	3	6	3	2	4	9	6	9	6	9	9	5	5	5	4	3	5	8	2	4	3	8	3
	Pre	8	5	0	1	0	0	9	7	0	6	9	0	6	9	-	4	7	7	9	9	9	9	9	0
21	Post	9	5	9	5	5	5	9	8	9	7	9	9	6	9	8	4	2	7	9	9	6	9	9	5
	Pre	9	9	5	5	3	3	9	9	9	9	9	9	5	9	0	7	6	9	9	9	9	9	9	0

TABLE II Contd.

Compd	Pre/ Post	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
22	Post	9	5	8	8	5	5	9	9	9	7	9	9	9	9	5	4	2	7	9	9	9	9	9	5
	Pre	9	9	5	8	2	5	9	9	9	9	9	9	9	9	3	8	9	9	9	9	9	9	9	3
23	Post	7	3	6	2	5	2	7	7	9	7	9	9	9	6	4	2	2	4	4	7	6	6	5	3
	Pre	9	7	2	3	0	0	9	7	9	8	9	9	5	9	-	2	2	5	5	9	8	9	9	3

TABLE III

Compd	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
24			2		3				9		9		8	9					8	9	5	5	7	2
25			3		2				9		9		9	9					7	9	8	9	9	0
26	9	9	2	5	0	3	9	7	9	-	9	9	3	9	1	6	9	6	9	9	9	9	6	2
27			2		2				9		9		3	7					9	9	8	9	9	3
28			2		0				9		9		3	8					8	6	3	8	3	0
29			2		0				9		9		2	2					0	4	2	7	0	0
30			0		0				5		0		0	0					0	0	0	5	0	0
31			0		6				0		0		2	3					0	0	0	0	0	0
32			2		0				9		9		2	9					6	9	9	9	9	0
33			0		0				9		9		0	3					5	9	4	9	4	0
34			0		0				8		8		0	3					3	8	0	7	0	0
35			0		0				5		3		0	0					0	0	0	0	0	0
36			0		0				6		3		0	0					2	0	0	6	0	0
37			0		0				8		8		0	0					0	3	0	0	0	0
38			0		0				8		6		0	0					0	0	0	0	0	0

TABLE III Continued

Compd	BV	BN	GM	ZM	OS	TA	PA	MI	CA	GA	AR	PO	IH	AT	XT	AF	AM	LR	SH	SV	BP	PD	EC	CE
39			2		0				9		9		2	9					6	9	6	9	5	0
40			2		0				7		9		0	4					0	6	0	3	0	0
41			0		3				9		9		0	6					5	9	2	9	0	0
42			0		2				5		8		0	0					0	0	0	0	0	0
43			0		1				1		5		0	0					0	0	0	0	0	0
44			0		0				5		5		0	0					0	5	3	0	3	0
45			0		2				0		0		0	0					0	0	0	0	0	0
46			0		0				0		0		0	0					0	0	0	0	0	0

TABLE IV

Abbreviations used for Test Plants

BV - Sugar beet

BN - Oil seed rape

GM - Soybean

ZM - Maize

OS - Rice

TA - Winter wheat

PA - *Polygonum aviculare*

CA - *Chenopodium album*

GA - *Galium aparine*

AR - *Amaranthus retroflexus*

MI - *Matricaria inodora*

BP - *Bidens pilosa*

PO - *Portulaca oleracea*

IH - *Ipomoea hederacea*

AT - *Abutilon theophrasti*

XT - *Xanthium strumarium*

AF - *Avena fatua*

AM - *Alopecurus myosuroides*

LR - *Lolium rigidum*

SH - *Sorghum halepense*

SV - *Setaria viridis*

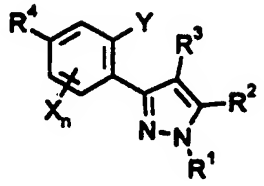
PD - *Panicum dichotomiflorum*

EC - *Echinochloa crus-galli*

CE - *Cyperus esculentus*

CLAIMS

1. A compound of general formula (I):



I

wherein:

R^1 is hydrogen or alkyl, alkenyl, alkynyl, benzyl, cycloalkyl or cycloalkenyl, any of which may optionally be substituted;

R^2 is alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or halo, OR^5, SO_mR^5, $O(alkyl)CO_2R^5$ or $O(alkyl)COR^5$;

m is 0, 1 or 2;

R^3 is H, halogen, cyano, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or SO_2Z, COR^5, CO_2R^5 or OR^5;

R^4 is H, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, or cyano, nitro, halogen, NR^5R^6, OR^5, SO_pR^5, CO_2R^5, $CONR^5R^6$, $NR^5SO_2R^6$, COR^5, $C(NOR^5)R^6$, OSO_pR^5, NR^5COR^6, $O(alkyl)COR^5$, $O(alkyl)CO_2R^5$ or SO_2Z;

Each X is independently halogen, cyano, nitro, alkyl, alkenyl or alkynyl, any of which may optionally be substituted, OR^5, NR^5R^6, $NR^5SO_2R^6$, OSO_2R^5, SO_pR^5, CO_2R^5, COR^5, NR^5COR^6, R^5OR^6, $CONR^5R^6$, SO_2Z or heterocyclyl or, alternatively two X groups or an X group and R^4 may together form a further ring;

Z is halogen;

p is 0, 1 or 2;

n is 0, 1, 2 or 3;

Y is halogen, cyano or optionally substituted alkoxy;

R^5 and R^6 are each independently H, alkyl, alkenyl or alkynyl, any of which may optionally be substituted.

2. A compound as claimed in claim 1, wherein, independently or in any combination:

R^1 is lower alkyl, particularly methyl or ethyl;

R^2 is a haloalkoxy or haloalkyl group;

R^3 is chlorine or bromine;

Y is chlorine or fluorine; and

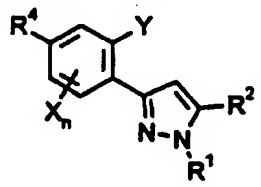
R^4 is cyano, bromo, methoxy, nitro or methylsulphonyl.

3. A compound as claimed in claim 1 or claim 2, wherein R^2 is a halogen-substituted methyl, ethyl, methoxy and ethoxy group.

4. A compound as claimed in any one of claims 1 to 3, wherein R^3 is chlorine and Y is fluorine.

5. Any one of Compounds 1 to 66 of Table I.

6. A process for the preparation of a compound as claimed in any one of claims 1 to 5, the process comprising the halogenation of compounds of formula (II):



II

in which R^1, R^2, R^4, X, Y and n are as defined in relation to formula (I).

7. A herbicidal composition comprising a compound as claimed in any one of claims 1 to 5 together with an agriculturally acceptable diluent or carrier.

8. A process for severely damaging or killing unwanted plants, the process comprising applying to the plants or to the growth medium of the plants, a compound as claimed in any one of claims 1 to 5.

9. A compound of general formula II as defined in claim 6.

FIGURE 1

REACTION SCHEME I

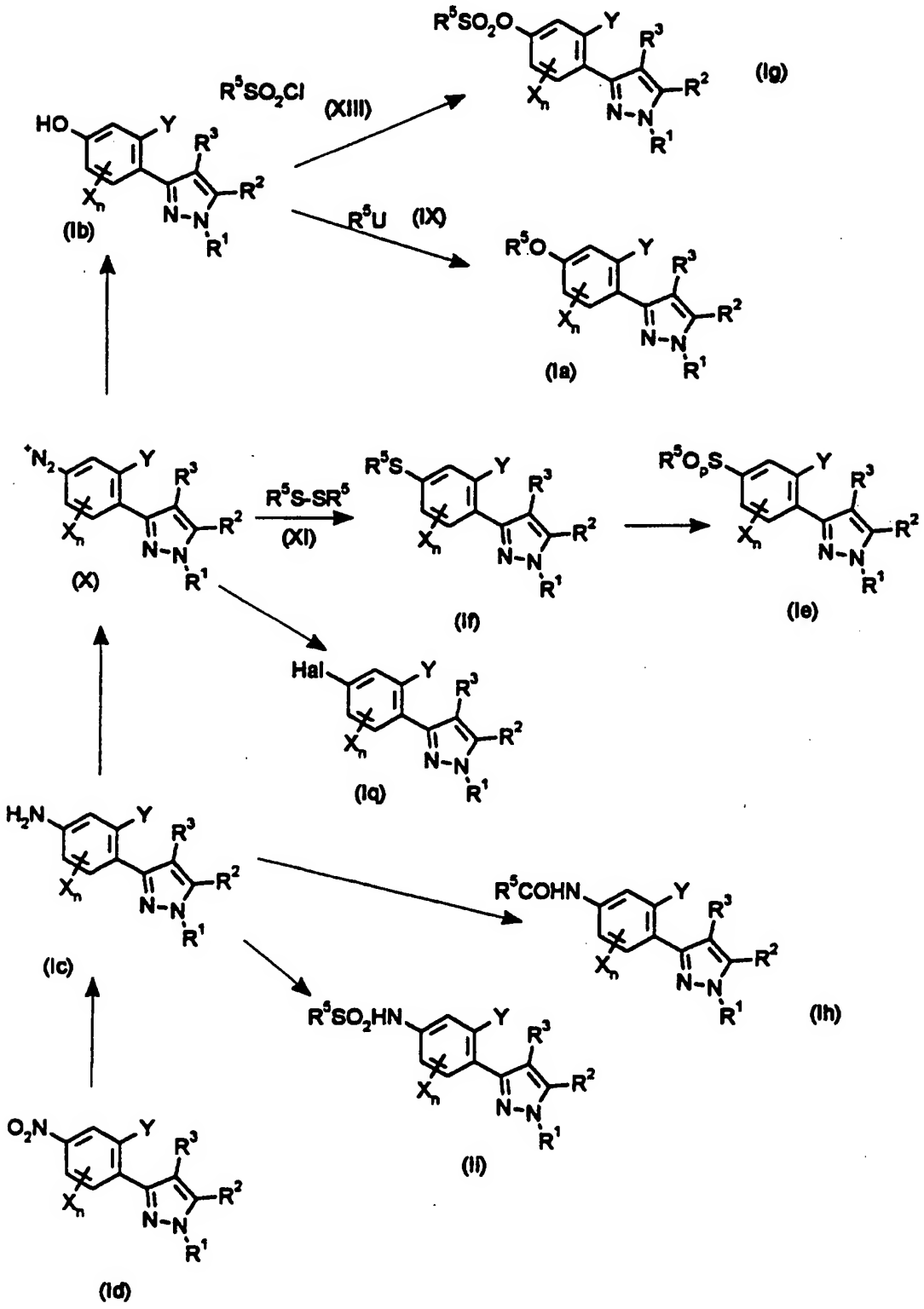


FIGURE 2

REACTION SCHEME II

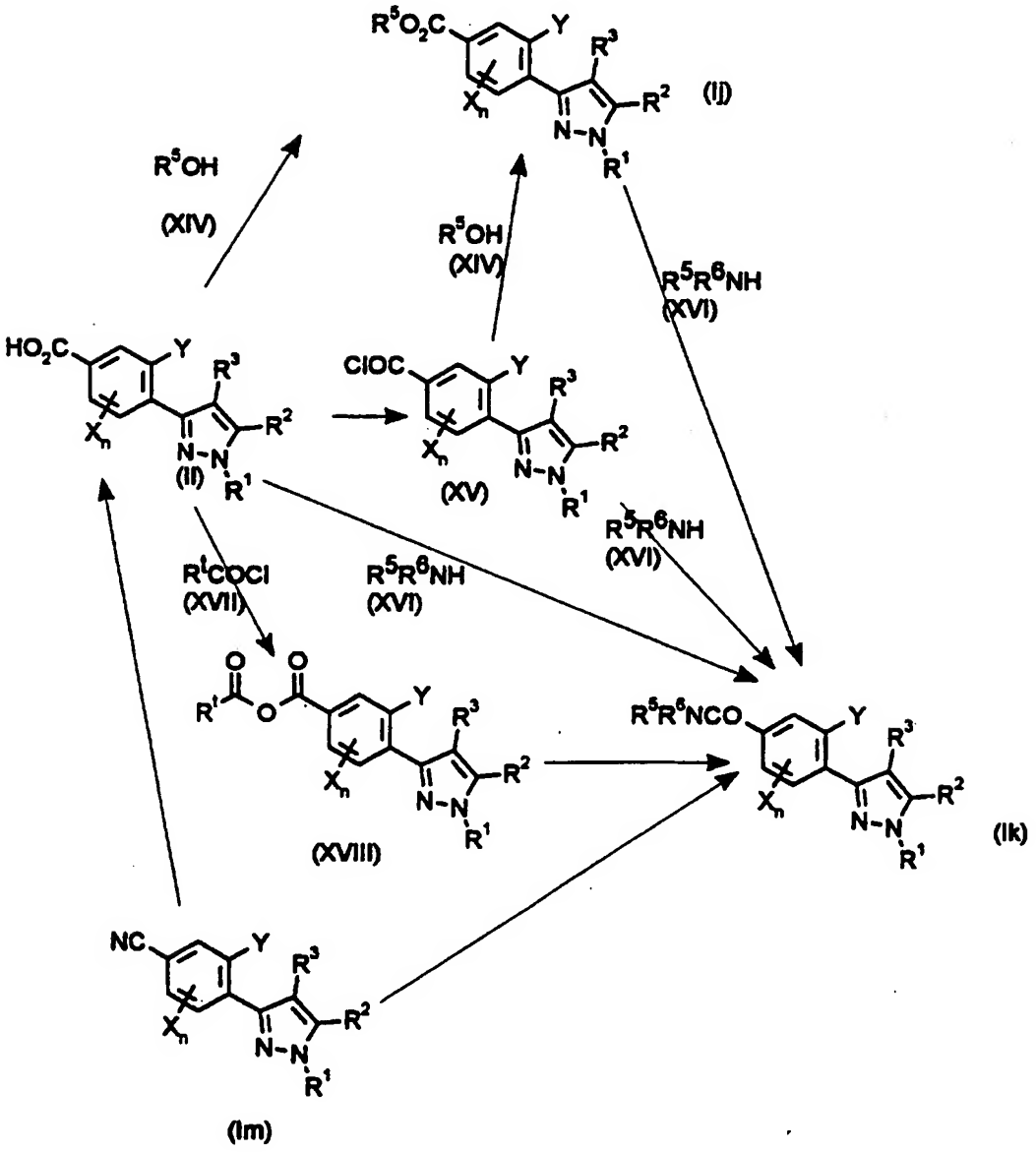
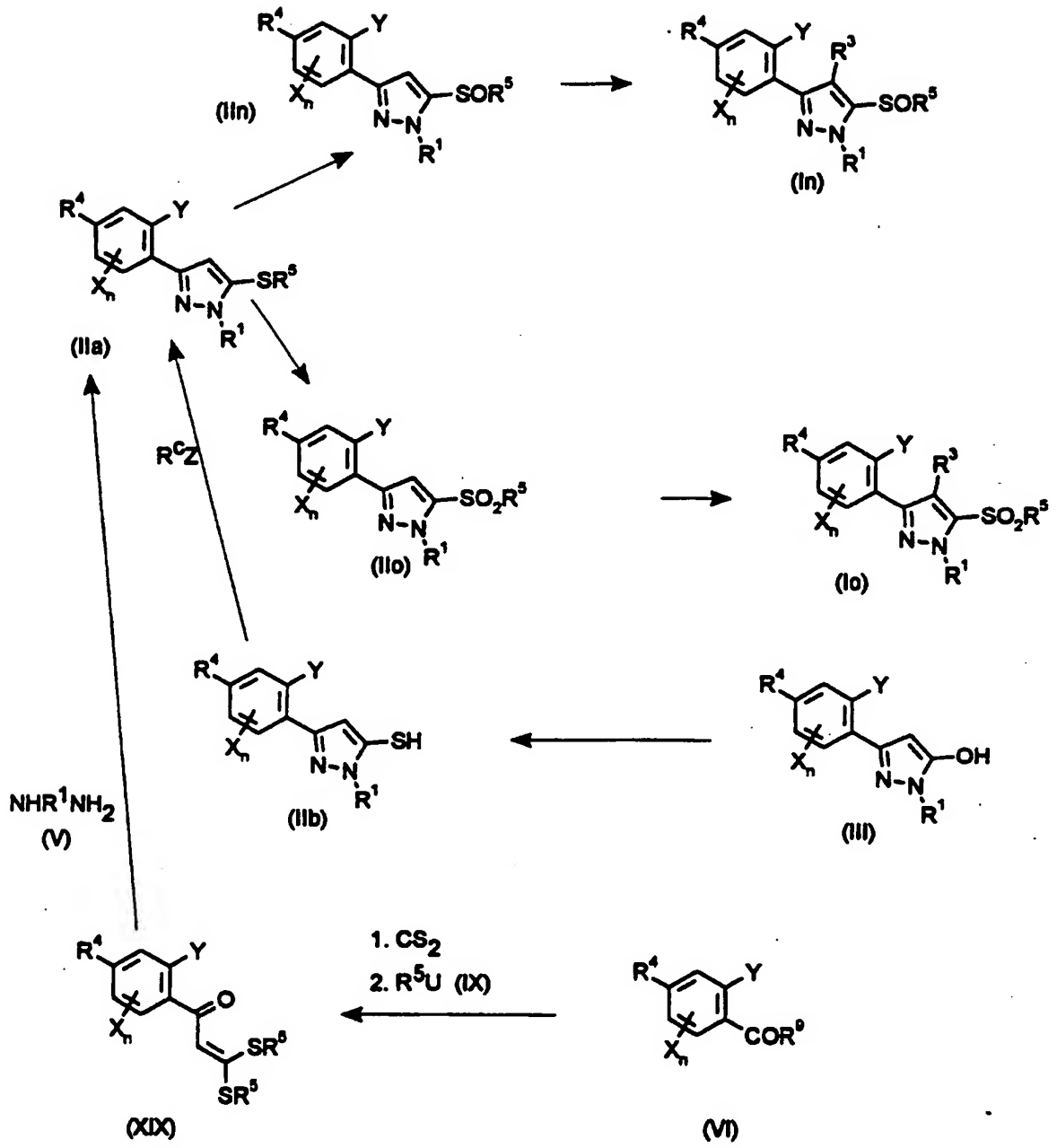


FIGURE 3

REACTION SCHEME III



INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 95/02458

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/20 C07D231/18 C07D231/16 A01N43/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 115, no. 5, 5 August 1991, Columbus, Ohio, US; abstract no. 49684h, J. MIURA ET AL. 'Preparation of 3-phenylpyrazole derivatives as herbicides.' page 849 ;column 1 ; see abstract; and Chemical Abstracts, CHEMICAL SUBSTANCES, 12th Collective Index, vol. 106-115, 1987-1991, pages 78277CS, 78279CS, 78529CS: RN[134793-06-9] ,[134793-04-7],[134793-01-4],[134793-15-0] & JP,A,03 072 460 (NIHON NOHIYAKU CO., LTD.) 27 March 1991 cited in the application	1-9

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

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'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

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'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 January 1996	19.01.1996

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Inter: al Application No
PCT/GB 95/02458

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,92 06962 (MONSANTO COMPANY) 30 April 1992 cited in the application see the whole document	1-9

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/GB 95/02458

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP-A-03072460	27-03-91	NONE	
WO-A-9206962	30-04-92	US-A- 5281571	25-01-94
		AU-B- 653758	13-10-94
		AU-B- 8927591	20-05-92
		BG-A- 97638	31-03-94
		CN-A- 1061777	10-06-92
		CN-A- 1090845	17-08-94
		EP-A- 0553307	04-08-93
		ES-T- 2059290	16-11-94
		FI-A- 931708	10-06-93
		HU-A- 64310	28-12-93
		JP-T- 6502637	24-03-94
		NZ-A- 240282	27-04-94
		SK-A- 35993	07-07-93